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NSAIDS

FIROX® (firocoxib) CHEWABLE TABLETS

Significant savings versus the pioneer product

Bioequivalent to Previcox® (firocoxib) Chewable Tablets

Chewable tablet for dogs with pork-liver flavoring

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

NSAIDS

LOXICOM® (meloxicam)

Bioequivalent to Metacam® (meloxicam)

For dogs, oral suspension or injectable solution for pain and inflammation due to osteoarthritis (OA)

For cats, injectable solution for pain and inflammation associated with some surgeries

Oral suspension does not contain xylitol and has no objectionable odor

1.5 mg/mL strength oral suspension in 10 mL, 32 mL, 100 mL and economical 2 x 100 mL bottles

5 mg/mL strength injection in 10 mL and 20 mL vials

NSAIDS

CARPRIEVE® (carprofen)

Bioequivalent to the pioneer NSAID Rimadyl® (carprofen)

Available in chewable tablets, caplets and injection for dogs

Significant savings versus the pioneer product

25 mg, 75 mg and 100 mg strength caplets or chewable tablets in 30, 60 and economical 180 count bottles

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ANTIBIOTICS

ENROFLOX® (enrofloxacin)

Same active ingredient and dosing regimen as Baytril® (enrofloxacin) Antibacterial products

Available in chewable tablets for dogs and cats and injection for dogs

Chewable tablets do not contain talc

22.7 mg, 68 mg and 136 mg strength chewable tablets in 50 and economical 200 count bottles

22.7 mg/mL strength injection in 20 mL, 50 mL and economical 100 mL vials

ANTIPARASITICS

SELARID® (selamectin)

Monthly topical antiparasitic

Treats fleas, prevents heartworm disease, and treats and controls several other common parasites in dogs and cats

Significant savings versus Revolution® (selamectin)

Clear applicators to ensure entire contents applied

Available in a variety of dosage strengths and applicator sizes corresponding to pet species and weight

ANTIPARASITICS

MIDAMOX® (imidacloprid + moxidectin) FOR DOGS & CATS

Monthly topical antiparasitic

Treats fleas, prevents heartworm disease, and treats and controls several other common parasites in dogs and cats

Significant savings versus Advantage Multi® for Dogs and Cats (imidacloprid + moxidectin)

Clear applicators to ensure entire contents applied

Available in a variety of dosage strengths and applicator sizes corresponding to pet species and weight

Enhancing Animal Health

Norbrook® is a world-class pharmaceutical solutions provider offering quality, cost-effective animal health products to the veterinary community.

Our innovative and research-based approach brings customer and market insights to life, and translates them into effective veterinary pharmaceuticals. Driven by an enterprising spirit, our attentive team of professionals is committed to helping you enhance the well-being of your clients, your community and yourself.

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To place an order, contact your distributor or Norbrook rep.

Firox® Chewable Tablets: 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.**

Loxicom® Oral Suspension 1.5 mg/mL: Observe label directions. **Do not use Loxicom Oral Suspension in cats. Acute renal failure and death have been associated with the use of meloxicam in cats.** As with any medication, side effects may occur. These are usually mild, but may be serious. The most common side effects reported in field studies were vomiting, soft stool/diarrhea and decreased appetite. If side effects occur, discontinue treatment immediately and consult a veterinarian. Dogs should be evaluated for pre-existing medical conditions prior to treatment and monitored during therapy. See product labeling for full product, safety and adverse event reporting information.

Loxicom® Solution for Injection 5 mg/mL:

Warning: Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. See the Contraindications, Warnings and Precautions section of the package insert for detailed information.

Loxicom (meloxicam) 5 mg/mL Injection is a non-steroidal anti-inflammatory prescription medication available only through a veterinarian. As with other NSAID-class medications, signs of meloxicam intolerance may include appetite loss, vomiting and diarrhea, which could indicate side effects involving the digestive tract, liver or kidneys. Some of these side effects may occur without warning and, in rare situations may be serious, resulting in hospitalization or even death. Observe the dog or cat for signs of potential drug toxicity. If these signs occur, discontinue meloxicam therapy and contact a veterinarian immediately. Loxicom should be administered to cats only via the subcutaneous (SQ) route. Do not use intravenously (IV) in cats. Concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. Do not administer a second dose of meloxicam to cats. Do not follow the single, one-time dose of meloxicam with any other NSAID or with meloxicam oral suspension in cats. Do not use meloxicam in cats with pre-existing renal dysfunction. Refer to the product insert for additional safety information (including warnings, precautions and contraindications) and full directions for use.

Carprieve® Family: IMPORTANT SAFETY INFORMATION As a class, NSAIDs may be associated with gastrointestinal, kidney and liver side effects. These are usually mild, but may be serious. Pet owners should discontinue therapy and contact their veterinarian immediately if side effects occur. Evaluation for pre-existing conditions and regular monitoring are recommended for pets on any medication, including CARPRIEVE. Use with other NSAIDs or corticosteroids should be avoided. See product labeling for full Prescribing Information.

Enroflox® Chewable Tablets: CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian. In rare instances, use of this product in cats has been associated with retinal toxicity. Do not exceed 2.27 mg/lb of body weight per day in cats. Observe label directions and see product labeling for full product information.

Enroflox® Injection for Dogs 2.27%: CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian. Federal law prohibits the extralabel use of this drug in food-producing animals. **CONTRAINDICATIONS:** Enrofloxacin is contraindicated in dogs known to be hypersensitive to quinolones. The safe use of enrofloxacin has not been established in large and giant breeds during the rapid growth phase. The use of enrofloxacin is contraindicated in small and medium breed dogs during the rapid growth phase (between 2 and 8 months of age). **WARNINGS: For use in animals only. The use of this product in cats may result in retinal toxicity. Keep out of reach of children.** Observe label directions and see product labeling for full product information.

Selarid®: IMPORTANT SAFETY INFORMATION: Do not use SELARID on sick, weak or underweight cats and dogs. Use only on cats 8 weeks and older and on dogs 6 weeks and older. Prior to administration, dogs should be tested for heartworms. Side Effects may include digestive upset and temporary hair loss at application site with possible inflammation. In people, SELARID may be irritating to skin and eyes. Wash hands after use. See Package Insert for full Prescribing Information.

Midamox® for Dogs and Cats: CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.
Dogs: WARNING: **DO NOT ADMINISTER THIS PRODUCT ORALLY.** For the first 30 minutes after application ensure that dogs cannot lick the product from application sites on themselves or other treated animals. Children should not come in contact with the application sites for two (2) hours after application. (See Contraindications, Warnings, Human Warnings, and Adverse Reactions for more information.) CONTRAINDICATIONS: Do not use this product on cats. **Cats and Ferrets:** WARNINGS: Do not use on sick or debilitated cats or ferrets. Do not use on underweight cats (see ADVERSE REACTIONS). Do not use on cats less than 9 weeks of age or less than 2 lbs. body weight. Do not use on ferrets less than 2 lbs. body weight. PRECAUTIONS: Avoid oral ingestion. HUMAN WARNINGS: Children should not come in contact with the application site for 30 minutes after application.

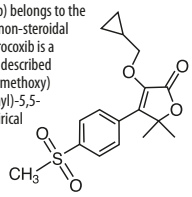
Firox™ (firocoxib)

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 $C_{17}H_{20}O_5S$, 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 (CLsystemic = ~0.4 L/hr/kg). Despite a high level of plasma protein binding (96%), firocoxib exhibits a large volume of distribution (Vd_{ss} 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 Firox 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: 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-tissure 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
SQ 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
Oozing 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 included the following stabilization procedures: fabellar suture and/or imbrication, fibular head transposition, tibial plateau leveling osteotomy (TPLO), and 'over 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 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 (1 X) 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 below 86° F (30° C). Brief excursions up to 104° F (40° C) are permitted. Use half tablet within 90 days.

To Request 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/anti-pyretic 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:
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1-866-591-5777
Approved by FDA under ANADA # 200-722

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Norbrook®

Professional Insert

Approved by FDA under ANADA # 200-497

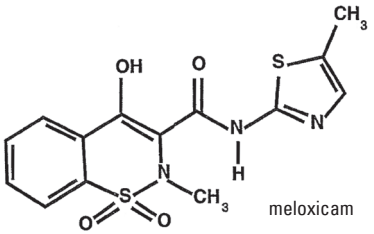
Loxicom®
(meloxicam oral suspension)
1.5 mg/mL

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.

Warning: Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. See Contraindications, Warnings, and Precautions for detailed information.

Description: Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. Each milliliter of Loxicom® Oral Suspension contains meloxicam equivalent to 1.5 milligrams and sodium benzoate (1.5 milligrams) as a preservative. The chemical name for Meloxicam is 4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carbox-amide-1, 1-dioxide. The formulation is a yellowish viscous suspension.



meloxicam

Indications: Loxicom Oral Suspension is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

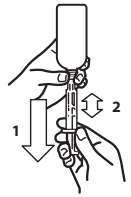
Dosage and Administration:
Always provide client information sheet with prescription. Carefully consider the potential benefits and risk of Loxicom Oral Suspension and other treatment options before deciding to use Loxicom Oral Suspension. Use the lowest effective dose for the shortest duration consistent with individual response. Loxicom Oral Suspension should be administered initially at 0.09 mg/lb (0.2 mg/kg) body weight only on the first day of treatment. For all treatments after day 1, Loxicom Oral Suspension should be administered once daily at a dose of 0.045 mg/lb (0.1 mg/ kg). The syringes are calibrated to deliver the daily maintenance dose in lbs. Because the first dose (0.2 mg/kg) is two times the amount of the daily maintenance dose (0.1 mg/kg), two syringes containing the 0.1 mg/kg dose should be administered at the first dose.

Directions for Administration:
Loxicom Oral Suspension is packaged with 2 sizes of dosing syringes. The small syringe is calibrated in 1-lb increments for use in dogs under 30 lbs. The large syringe is calibrated in 5-lb increments (up to 160 lbs.) and should be used for dosing dogs that are 30 lbs and over. **Only administer Loxicom with the provided syringes. The container should never be used as a dropper bottle for administration of Loxicom.**

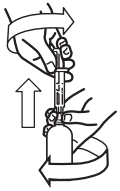
Dogs under 30 lbs (13.6 kg)
Shake well before use, then remove cap. Loxicom Oral Suspension can be given either mixed with food or placed directly into the mouth. Particular care should be given with regard to the accuracy of dosing. **To prevent accidental overdosing of small dogs, only use the small dosing syringe.** The large syringe provided should not be used to measure doses for dogs weighing less than 30 lbs (13.6 kg). For dogs under 30 lbs, use the small dosing syringe provided in the package (see dosing procedure below). The small dosing syringe fits onto the bottle and has dosing marks in 1-lb increments, designed to deliver the daily maintenance dose of 0.045 mg/lb (0.1 mg/kg). For dogs between 1 - 29 lbs, Loxicom can be given using the marks on the small dosing syringe. When using the small dosing syringe, the dog's weight should be rounded down to the nearest 1-lb increment. Replace and tighten cap after use.

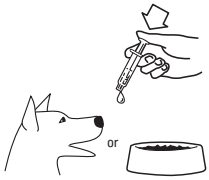
Dogs 30 lbs (13.6 kg) and over
Shake well before use, then remove cap. Loxicom may be either mixed with food or placed directly into the mouth. Particular care should be given with regard to the accuracy of dosing. **To prevent accidental overdosing of small dogs, do not use the large syringe in animals weighing less than 30 pounds.** For dogs 30 lbs or greater, the large dosing syringe provided in the package should be used (see dosing procedure below). The large dosing syringe fits onto the bottle and has dosing marks in 5-lb increments (up to 160 lbs), designed to deliver the daily maintenance dose of 0.045 mg/lb (0.1 mg/kg). When using the large syringe, the dog's weight should be rounded down to the nearest 5-lb increment. Replace and tighten cap after use.

Shake bottle well. Push down and unscrew bottle top. Attach the dosing syringe to the bottle by gently pushing the end onto the top of the bottle.



Turn the bottle/syringe upside down. Pull the plunger out until the medication level corresponds to the dog's body weight in pounds.


Turn the bottle right way up and with a twisting movement separate the dosing syringe from the bottle.



Push the plunger to empty the contents of the syringe on food or directly in the mouth.

Contraindications: Dogs with known hypersensitivity to meloxicam should not receive Loxicom Oral Suspension. **Do not use Loxicom Oral Suspension in cats. Acute renal failure and death have been associated with the use of meloxicam in cats.**

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.
As with any NSAID all dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory testing to establish hematological and serum biochemical baseline data is recommended prior to and periodically during administration. Owner should be advised to observe their dog for signs of potential drug toxicity and be given a client information sheet about Loxicom.

Precautions: The safe use of Loxicom Oral Suspension in dogs younger than 6 months of age, dogs used for breeding, or in pregnant or lactating dogs has not been evaluated. Meloxicam is not recommended for use in dogs with bleeding disorders, as safety has not been established in dogs with these disorders. As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal 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 renal toxicity 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. 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 induce gastrointestinal ulcerations and/or perforations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. If additional pain medication is needed after administration of the total daily dose of Loxicom Oral Suspension, a non-NSAID or non-corticosteroid class of analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from corticosteroid use or from one NSAID to another in dogs. The use of concomitantly protein-bound drugs with Loxicom Oral Suspension 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 Loxicom Oral Suspension has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

Adverse Reactions: Field safety was evaluated in 306 dogs. Based on the results of two studies, GI abnormalities (vomiting, soft stools, diarrhea, and inappetance) were the most common adverse reactions associated with the administration of meloxicam. The following table lists adverse reactions and the numbers of dogs that experienced them during the studies. Dogs may have experienced more than one episode of the adverse reaction during the study.

Adverse Reactions Observed During Two Field Studies		
Clinical Observation	Meloxicam (n=157)	Placebo (n=149)
Vomiting	40	23
Diarrhea/Soft Stool	19	11
Bloody Stool	1	0
Inappetance	5	1
Bleeding gums after dental procedure	1	0
Lethargy/Swollen Carpus	1	0
Epiphora	1	0

In foreign suspected adverse drug reaction (SADR) reporting over a 9 year period, incidences of adverse reactions related to meloxicam administration included: auto-immune hemolytic anemia (1 dog), thrombocytopenia (1 dog), polyarthritis (1 dog), nursing puppy lethargy (1 dog), and pyoderma (1 dog).

Post-Approval Experience (Rev. 2010): The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse reactions are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of frequency by body system.

Gastrointestinal: vomiting, anorexia, diarrhea, melena, gastrointestinal ulceration
Urinary: azotemia, elevated creatinine, renal failure
Neurological/Behavioral: lethargy, depression
Hepatic: elevated liver enzymes
Dermatologic: pruritus

Death has been reported as an outcome of the adverse events listed above. **Acute renal failure and death have been associated with use of meloxicam in cats.** 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
Loxicom, 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 Loxicom 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: Meloxicam has nearly 100% bioavailability when administered orally with food. The terminal elimination half-life after a single dose is estimated to be approximately 24 hrs (+/-30%) regardless of route of administration. There is no evidence of statistically significant gender differences in drug pharmacokinetics. Drug bioavailability, volume of distribution, and total systemic clearance remain constant up to 5 times the recommended dose for use in dogs. However, there is some evidence of enhanced drug accumulation and terminal elimination half-life prolongation when dogs are dosed for 45 days or longer.
Peak drug concentrations can be expected to occur within about 7.5 hrs after oral administration. Corresponding peak concentration is approximately 0.464 mcg/mL following a 0.2 mg/kg oral dose. The drug is 97% bound to canine plasma proteins.

Effectiveness: The effectiveness of meloxicam was demonstrated in two field studies involving a total of 277 dogs representing various breeds, between six months and sixteen years of age, all diagnosed with osteoarthritis. Both of the placebo-controlled, masked studies were conducted for 14 days. All dogs received 0.2 mg/kg on day 1. All dogs were maintained on 0.1 mg/kg oral meloxicam from days 2 through 14 of both studies. Parameters evaluated by veterinarians included lameness, weight-bearing, pain on palpation, and overall improvement. Parameters assessed by owners included mobility, ability to rise, limping, and overall improvement. In the first field study (n=109), dogs showed clinical improvement with statistical significance after
14 days of meloxicam treatment for all parameters. In the second field study (n=48), dogs receiving meloxicam showed a clinical improvement after 14 days of therapy for all parameters; however, statistical significance was demonstrated only for the overall investigator evaluation on day 7, and for the owner evaluation on day 14.

Safety:
Six Week Study
In a six week target animal safety study, meloxicam was administered orally at 1, 3, and 5X the recommended dose with no significant clinical adverse reactions. Animals in all dose groups (control, 1, 3 and 5X the recommended dose) exhibited some gastrointestinal distress (diarrhea and vomiting). No treatment-related changes were observed in hematological, blood chemistry, urinalysis, clotting time, or buccal mucosal bleeding times. Necropsy results included stomach mucosal petechiae in one control dog, two dogs at the 3X and one dog at the 5X dose. Other macroscopic changes included areas of congestion or depression of the mucosa of the jejunum or ileum in three dogs at the 1X dose and in two dogs at the 5X dose. Similar changes were also seen in two dogs in the control group. There were no macroscopic small intestinal lesions observed in dogs receiving the 3X dose. Renal enlargement was reported during the necropsy of two dogs receiving the 3X and two receiving the 5X dose.
Microscopic examination of the kidneys revealed minimal degeneration or slight necrosis at the tip of the papilla in three dogs at the 5X dose. Microscopic examination of the stomach showed inflammatory mucosal lesions, epithelial regenerative hyperplasia or atrophy, and submucosal gland inflammation in two dogs at the recommended dose, three dogs at the 3X and four dogs at the 5X dose. Small intestinal microscopic changes included minimal focal mucosal erosion affecting the villi, and were sometimes associated with mucosal congestion. These lesions were observed in the ileum of one control dog and in the jejunum of one dog at the recommended dose and two dogs at the 5X dose.
Six Month Study
In a six month target animal safety study, meloxicam was administered orally at 1, 3, and 5X the recommended dose with no significant clinical adverse reactions. All animals in all dose groups (controls, 1, 3, and 5X the recommended dose) exhibited some gastrointestinal distress (diarrhea and vomiting). Treatment related changes seen in hematology and chemistry included decreased red blood cell counts in seven of 24 dogs (four 3X and three 5X dogs), decreased hematocrit in 18 of 24 dogs (including three control dogs), dose-related neutrophilia in one 1X, two 3X and three 5X dogs, evidence of regenerative anemia in two 3X and one 5X dog. Also noted were increased BUN in two 5X dogs and decreased albumin in one 5X dog.
Endoscopic changes consisted of reddening of the gastric mucosal surface covering less than 25% of the surface area. This was seen in three dogs at the recommended dose, three dogs at the 3X dose and two dogs at the 5X dose. Two control dogs exhibited reddening in conjunction with ulceration of the mucosa covering less than 25% of the surface area.
Gross gastrointestinal necropsy results observed included mild discoloration of the stomach or duodenum in one dog at the 3X and in one dog at the 5X dose. Multifocal pinpoint red foci were observed in the gastric fundic mucosa in one dog at the recommended dose, and in one dog at the 5X dose.
No macroscopic or microscopic renal changes were observed in any dogs receiving meloxicam in this six month study. Microscopic gastrointestinal findings were limited to one dog at the recommended dose, and two dogs at the 3X dose. Mild inflammatory mucosal infiltrate was observed in the duodenum of one dog at the recommended dose. Mild congestion of the fundic mucosa and mild myositis of the outer mural musculature of the stomach were observed in two dogs receiving the 3X dose.

How Supplied:
Loxicom Oral Suspension 1.5 mg/mL: 10, 32 and 100 mL bottles with small and large dosing syringes.

Storage: Store at controlled room temperature 68-77°F (20-25°C). Excursions permitted between 59°F and 86°F (15°C and 30°C). Brief exposure to temperature up to 104° F (40°C) may be tolerated provided the mean kinetic temperature does not exceed 77°F (25°C); however such exposure should be minimized.

TAKE TIME

OBSERVE LABEL DIRECTIONS

Made in the UK.

Manufactured by:
Norbrook Laboratories Limited
Newry, BT35 6PU, Co. Down, Northern Ireland

Loxicom® is a registered trademark of Norbrook Laboratories Limited

U.S. Patent No. 9,399,013

Rev. 03/21
083670I02

Norbrook®

Package Insert for Dogs

Approved by FDA under ANADA # 200-491

Loxicom®

(meloxicam)

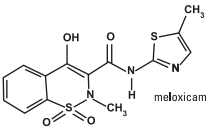
5 mg/mL Solution for Injection

Non-steroidal anti-inflammatory drug for use in dogs and cats only.

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

Warning: Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. See Contraindications, Warnings, and Precautions for detailed information.

Description:
Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. Each mL of this sterile product for injection contains meloxicam 5.0 mg, alcohol 15%, glycofurol 10%, poloxamer 188 5%, sodium chloride 0.6%, glycine 0.5% and meglumine 0.3%, in water for injection, pH adjusted with sodium hydroxide and hydrochloric acid.



meloxicam

Indications:
Dogs: Loxicom® (meloxicam) 5 mg/mL Solution for Injection is indicated in dogs for the control of pain and inflammation associated with osteoarthritis.

Dosage and Administration:
Carefully consider the potential benefits and risk of Loxicom and other treatment options before deciding to use Loxicom. Use the lowest effective dose for the shortest duration consistent with individual response.

Dogs: Loxicom 5 mg/mL Solution for Injection should be administered initially as a single dose at 0.09 mg/lb (0.2 mg/kg) body weight intravenously (IV) or subcutaneously (SQ), followed, after 24 hours, by Loxicom Oral Suspension at the daily dose of 0.045 mg/lb (0.1 mg/kg) body weight, either mixed with food or placed directly in the mouth.

Contraindications:
Dogs with known hypersensitivity to meloxicam should not receive Loxicom 5 mg/mL Solution for Injection.

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 IV or SQ injectable use in dogs. All dogs should undergo a thorough history and physical examination before administering any NSAID. Appropriate laboratory testing to establish hematological and serum biochemical baseline data is recommended prior to, and periodically during use of any NSAID in dogs.
Owner should be advised to observe their dogs for signs of potential drug toxicity.

Precautions:
The safe use of Loxicom 5 mg/mL Solution for Injection in dogs younger than 6 months of age, dogs used for breeding, or in pregnant or lactating bitches has not been evaluated. Meloxicam is not recommended for use in dogs with bleeding disorders, as safety has not been established in dogs with these disorders. Safety has not been established for intramuscular (IM) administration in dogs. When administering Loxicom 5 mg/mL Solution for Injection, use a syringe of appropriate size to ensure precise dosing. As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal 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 renal toxicity 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. 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 induce gastrointestinal ulcerations and/or perforations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. If additional pain medication is needed after the administration of the total daily dose of meloxicam oral suspension, a non-NSAID or noncorticosteroid class of analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from corticosteroid use or from one NSAID to another in dogs. The use of concomitantly protein-bound drugs with Loxicom 5 mg/mL Solution for Injection 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 Loxicom 5 mg/mL Solution for Injection has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy. The effect of cyclo-oxygenase inhibition and the potential for thromboembolic occurrence or a hypercoagulable state has not been studied.

Adverse Reactions:
Dogs: A field study involving 224 dogs was conducted. Based on the results of this study, GI abnormalities (vomiting, soft stools, diarrhea, and inappetance) were the most common adverse reactions associated with the administration of meloxicam. The following table lists adverse reactions and the numbers of dogs that experienced them during the study. Dogs may have experienced more than one episode of the adverse reaction during the study.

Adverse Reactions Observed During Field Study

Clinical Observation	Meloxicam (n=109)	Placebo (n=115)
Vomiting	31	15
Diarrhea/Soft Stool	15	11
Inappetance	3	0
Bloody Stool	1	0

In foreign suspected adverse drug reaction (SADR) reporting, adverse reactions related to meloxicam administration included: auto-immune hemolytic anemia (1 dog), thrombocytopenia (1 dog), polyarthritis (1 dog), nursing puppy lethargy (1 dog), and pyoderma (1 dog).

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, diarrhea, melena, gastrointestinal ulceration*
Urinary: *azotemia, elevated creatinine, renal failure*
Neurological/Behavioral: *lethargy, depression*
Hepatic: *elevated liver enzymes*
Dermatologic: *pruritis*

Death has been reported as an outcome of the adverse events listed above. **Acute renal failure and death have been associated with the use of meloxicam in cats.** 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:
Meloxicam, like other NSAIDs, 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 NSAID intolerance. Adverse reactions may include vomiting, diarrhea, lethargy, decreased appetite and behavioral changes.
Dog owners should be advised when their pet has received a meloxicam injection. Dog owners should contact their veterinarian immediately if possible adverse reactions are observed, and dog owners should be advised to discontinue Loxicom therapy.

Clinical Pharmacology:
Meloxicam has nearly 100% bioavailability when administered orally or after subcutaneous injection in dogs. The terminal elimination half-life after a single dose is estimated to be approximately 24 hrs (+/-30%) in dogs regardless of route of administration. Drug bioavailability, volume of distribution, and total systemic clearance remain constant up to 5 times the recommended dose for use in dogs. However, there is some evidence of enhanced drug accumulation and terminal elimination half-life prolongation when dogs are dosed for 45 days or longer.
Peak drug concentrations of 0.734 mcg/mL can be expected to occur within 2.5 hours following a 0.2 mg/kg subcutaneous injection in dogs. Based upon intravenous administration in Beagle dogs, the meloxicam volume of distribution in dogs ($V_{d\lambda}$) is approximately 0.32 L/kg and the total systemic clearance is 0.01 L/hr/kg. The drug is 97% bound to canine plasma proteins.

Effectiveness:
Dogs: The effectiveness of meloxicam injection was demonstrated in a field study involving a total of 224 dogs representing various breeds, all diagnosed with osteoarthritis. This placebo-controlled, masked study was conducted for 14 days. Dogs received a subcutaneous injection of 0.2 mg/kg meloxicam injection on day 1. The dogs were maintained on 0.1 mg/kg oral meloxicam from days 2 through 14. Variables evaluated by veterinarians included lameness, weight-bearing, pain on palpation, and overall improvement. Variables assessed by owners included mobility, ability to rise, limping, and overall improvement.
In this field study, dogs showed clinical improvement with statistical significance after 14 days of meloxicam treatment for all variables.

Animal Safety:
Dogs: 3 Day Target Animal Safety Study - In a three day safety study, meloxicam injection was administered intravenously to Beagle dogs at 1, 3, and 5 times the recommended dose (0.2, 0.6 and 1.0 mg/kg) for three consecutive days. Vomiting occurred in 1 of 6 dogs in the 5X group. Fecal occult blood was detected in 3 of 6 dogs in the 5X group. No clinically significant hematologic changes were seen, but serum chemistry changes were observed. Serum alkaline phosphatase (ALP) was significantly increased in one 1X dog and two of the 5X dogs. One dog in the 5X group had a steadily increasing GGT over 4 days, although the values remained within the reference range. Decreases in total protein and albumin occurred in 2 of 6 dogs in the 3X group and 3 of 6 dogs in the 5X group. Increases in blood urea nitrogen (BUN) occurred in 3 of 6 dogs in the 1X group, 2 of 6 dogs in the 3X group and 2 of 6 dogs in the 5X group. Increased creatinine occurred in 2 dogs in the 5X group. Increased urine protein excretion was noted in 2 of 6 dogs in the control group, 2 of 6 dogs in the 1X group, 2 of 6 dogs in the 3X group, and 5 of 6 dogs in the 5X group. Two dogs in the 5X group developed acute renal failure by Day 4. Bicarbonate levels were at or above normal levels in 1 of the 3X dogs and 2 of the 5X dogs. Histological examination revealed gastrointestinal lesions ranging from superficial mucosal hemorrhages and congestion to erosions. Mesenteric lymphadenopathy was identified in 2 of 6 dogs in the 1X group, 4 of 6 dogs in the 3X group, and 5 of 6 dogs in the 5X group. Renal changes ranged from dilated medullary and cortical tubules and inflammation of the interstitium, to necrosis of the tip of the papilla in 2 of 6 dogs in the 1X group, 2 of 6 dogs in the 3X group, and 4 of 6 dogs in the 5X group.

Injection Site Tolerance – Meloxicam injection was administered once subcutaneously to Beagle dogs at the recommended dose of 0.2 mg/kg and was well-tolerated by the dogs. Pain upon injection was observed in one of eight dogs treated with meloxicam. No pain or inflammation was observed post injection. Long term use of meloxicam injection in dogs has not been evaluated.

Effect on Buccal Mucosal BleedingTime (BMBT) – Meloxicam injection (0.2 mg/kg) and placebo (0.4 mL/kg) were administered as single intravenous injections to 8 female and 16 male Beagle dogs. There was no statistically significant difference ($p>0.05$) in the average BMBT between the two groups.

Storage Information:
Store at controlled room temperature, 68-77°F (20-25°C). Use within 180 days of first puncture and puncture a maximum of 51 times.

How Supplied:
Loxicom 5 mg/mL Solution for Injection: 10 mL and 20 mL vial

Made in the UK.

Norbrook Laboratories Limited
Newry, BT35 6PU, Co. Down, Northern Ireland

Rev. 06/2021

318670103

Norbrook®

Package Insert for Cats

Approved by FDA under ANADA # 200-491

Loxicom®

(meloxicam)

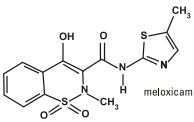
5 mg/mL Solution for Injection

Non-steroidal anti-inflammatory drug for use in dogs and cats only.

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

Warning: Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. See Contraindications, Warnings, and Precautions for detailed information.

Description: Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. Each mL of this sterile product for injection contains meloxicam 5.0 mg, alcohol 15%, glycofurol 10%, poloxamer 188 5%, sodium chloride 0.6%, glycine 0.5% and meglumine 0.3%, in water for injection, pH adjusted with sodium hydroxide and hydrochloric acid.



meloxicam

Indications:
Cats: For the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration when administered prior to surgery.

Dosage and Administration:
Carefully consider the potential benefits and risk of Loxicom and other treatment options before deciding to use Loxicom. Use the lowest effective dose for the shortest duration consistent with individual response.

Cats: Administer **a single, one-time subcutaneous dose** of Loxicom® 5 mg/mL Solution for Injection to cats at a dose of 0.14 mg/lb (0.3 mg/kg) body weight. **Use of additional meloxicam or other NSAIDs is contraindicated. (See Contraindications).** To ensure accuracy of dosing, the use of a 1 mL graduated syringe is recommended.

Contraindications: Cats with known hypersensitivity to meloxicam should not receive Loxicom 5 mg/mL Solution for Injection. Additional doses of meloxicam or other NSAIDs in cats are contraindicated, as no safe dosage for repeated NSAID administration has been established **(See Animal Safety). Do not use meloxicam in cats with pre-existing renal dysfunction.**

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 subcutaneous (SQ) injectable use in cats. Do not use IV in cats.

Do not administer a second dose of meloxicam.
Do not follow the single, one-time dose of meloxicam with any other NSAID. Do not administer meloxicam oral suspension following the single, one-time injectable dose of meloxicam.

When administering any NSAID, appropriate laboratory testing to establish hematological and serum biochemical baseline data is recommended prior to use in dogs and cats. All cats should undergo a thorough history and physical examination before administering meloxicam. **Do not repeat the single, one-time dose of meloxicam in cats. Owner should be advised to observe their cats for signs of potential drug toxicity.**

Precautions:
The safe use of Loxicom 5 mg/mL Solution for Injection in cats younger than 4 months of age, cats used for breeding, or in pregnant or lactating queens has not been evaluated.
Meloxicam is not recommended for use in cats with bleeding disorders, as safety has not been established in cats with these disorders. Safety has not been established for intravenous (IV) or intramuscular (IM) use in cats. When administering Loxicom 5 mg/mL Solution for Injection, use a syringe of appropriate size to ensure precise dosing.
As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal, and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Cats that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. 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. **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. **Anesthetic drugs may affect renal perfusion; approach concomitant use of anesthetics and NSAIDs cautiously. Appropriate monitoring procedures should be employed during all surgical procedures. The use of perioperative parenteral fluids is recommended to decrease potential renal complications when using NSAIDs. If additional pain medication is needed after the single one-time dose of meloxicam, a non-NSAID class of analgesic may be necessary.**
In one study[1], one cat in each NSAID treatment group had increased intraoperative hemorrhage. Since NSAIDs possess the potential to induce gastrointestinal ulcerations and/or gastrointestinal perforation, concomitant use of meloxicam with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided.
Consider appropriate washout times when switching from corticosteroid use to meloxicam in cats. **As a single use product in cats, meloxicam should not be followed by additional NSAIDs or corticosteroids.**
The use of concomitantly protein-bound drugs with Loxicom 5 mg/mL Solution for Injection has not been studied in cats. Commonly used protein-bound drugs include cardiac, anticonvulsant, and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of Loxicom 5 mg/mL Solution for Injection has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.
The effect of cyclo-oxygenase inhibition and the potential for thromboembolic occurrence or a hyper-coagulable state has not been studied.

Adverse Reactions:
Cats: A field study involving 138 cats was conducted. Of the 72 cats receiving meloxicam injection, six cats (8.3%) experienced post-treatment elevated serum blood urea nitrogen (BUN) levels. The pre-treatment values were in the normal range. Of the 66 cats in the buторphanol treatment group, no cats experienced post-treatment elevated serum blood urea nitrogen levels. Nine cats (12.5%) receiving meloxicam injection had post-treatment anemia. Pre-treatment, these cats all had hematocrit and hemoglobin values in the normal range. Four cats (6.1 %) in the butorphanol treatment group had post-treatment anemia. All but one cat, who had a mild anemia pre-treatment (hematocrit=21% and hemoglobin=7.0 g/dL) had normal pre-treatment values. Twenty-four hours after the injection with meloxicam injection, one cat experienced pain upon palpation of the injection site.

Foreign Experience:
Repeated use in cats has been associated with acute renal failure and death. In studies used for the foreign approval of meloxicam injection in cats, lethargy, vomiting, inappetance, and transient pain immediately after injection were noted. Diarrhea and fecal occult blood have also been reported.

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:

Urinary: *azotemia, elevated creatinine, elevated phosphorus, renal failure*
Gastrointestinal: *anorexia, vomiting, diarrhea*
Neurologic/Behavioral: *lethargy, depression*
Hematologic: *anemia*

Death has been reported as an outcome of the adverse events listed above. **Acute renal failure and death have been associated with the use of meloxicam in cats.**
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 Cat Owners: Meloxicam, like other NSAIDs, 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 NSAID intolerance. Adverse reactions may include vomiting, diarrhea, lethargy, decreased appetite and behavioral changes.
Cat owners should be advised when their pet has received a meloxicam injection.
Cat owners should contact their veterinarian immediately if possible adverse reactions are observed.

Clinical Pharmacology: Meloxicam has nearly 100% bioavailability after subcutaneous injection in cats. The terminal elimination half-life after a single dose is estimated to be approximately 15 hrs (+/-10%) in cats. Peak drug concentrations of 1.1 mcg/mL can be expected to occur within 1.5 hours following a 0.3 mg/kg subcutaneous injection in cats. The volume of distribution (V_d) in cats is approximately 0.27 L/kg, with an estimated total systemic clearance of 0.013 L/hr/kg. The drug is 97% bound to feline plasma proteins.

Effectiveness:
Cats: The effectiveness of meloxicam injection was demonstrated in a masked field study involving a total of 138 cats representing various breeds. This study used buторphanol as an active control. Cats received either a single subcutaneous injection of 0.3 mg/kg meloxicam injection or 0.4 mg/kg buторphanol prior to ovnychectomy, either alone or in conjunction with surgical neutering. All cats were premedicated with acepromazine, induced with propofol and maintained on isoflurane. Pain assessment variables evaluated by veterinarians included additional pain intervention therapy, gait/lameness score, analgesia score, sedation score, general impression score, recovery score, and visual analog scale score. Additionally, a cumulative pain score, which was the summation of the analgesia, sedation, heart rate and respiratory rate scores was evaluated.
A palpometer was used to quantify the pain threshold.
A substantial number of cats required additional intervention in the 0-24 hour post-surgical period, with the majority of these interventions taking place within the first hour. Therefore, the percentage of cats in each group that received one or more interventions was designated as the primary assessment variable. Approximately half of the cats in each group received a pain intervention as a result of the first (time 0) post-surgical evaluation, i.e., extubation. At this point, the need to provide a pain intervention was not statistically significant between the two groups (p=0.7215). However, the median number of interventions was one per cat in the meloxicam group and two per cat in the buторphanol group and this difference was statistically significant (p=.0.0021). The statistical evaluation supports the conclusion that the meloxicam test article is non-inferior to the buторphanol active control. Forty-eight of the 72 cats in the meloxicam group received one or more interventions (66.7%), and 47 of 66 cats in the buторphanol group received one or more interventions (71.2%). The number of interventions administered to the meloxicam group was less than the buторphanol group at 1, 3, 5, 8, 12, and 24 hours post-surgery.
Cats receiving meloxicam injection showed improvement in the pain assessment variables.

Animal Safety:
Cats: 3 Day Target Animal Safety Study - In a three day safety study, subcutaneous meloxicam injection administration to healthy cats at up to 1.5 mg/kg (5X the recommended dose) resulted in vomiting in three cats (1 of 6 control cats and 2 of 6 cats in 5X) and loose stools in four cats (2 of 6 control cats and 2 of 6 cats in 5X). Fecal occult blood was detected in ten of the twenty four cats, including two cats in the control group. This was not a dose-related event.
Clinically significant hematologic changes seen included increased PT and APTT in two cats (1 of 6 control cats and 1 of 6 cats in 5X), and elevated white blood cell counts in cats having renal or GI tract lesions. Serum chemistry changes observed included decreased total protein in four of 24 cats (1 of 6 cats in 1X, 2 of 6 cats in 3X and 1 of 6 cats in 5X), concomitant increases in blood urea nitrogen (BUN) and creatinine values in 2 of 6 cats in 5X.

Histological examination revealed gastrointestinal lesions ranging from inflammatory cell infiltration of the mucosa of the GI tract to erosions. Mesenteric lymphadenopathy was identified in 1 of 6 cats in 1X. Renal changes ranged from dilated medullary (2 of 6 cats in 1X, 1 of 6 cats in 3X, and 1 of 6 cats in 5X) and cortical (3 of 6 cats in 1X, 1 of 6 cats in 3X, and 3 of 6 cats in 5X) tubules and inflammation (2 of 6 cats in 1X, 2 of 6 cats in 3X, and 2 of 6 cats in 5X) or fibrosis (2 of 6 cats in 3X and 2 of 6 cats in 5X) of the interstitium to necrosis of the tip of the papilla (5 of 6 cats in 5X).

Subsequent oral dosing - In a nine day study with three treatment groups, meloxicam injection was given as a single subcutaneous injection using doses of 0 mg/kg (saline injection), 0.3 mg/kg and 0.6 mg/kg on Day 0. Meloxicam oral suspension, 1.5 mg/mL or saline was then administered orally once-daily at the same respective dose (0.3 or 0.6 mg/kg) for eight consecutive days. Clinical adverse reactions included vomiting, diarrhea, lethargy, and decreased food consumption in the treated groups, and one day of diarrhea in one control cat. The gross necropsy report includes observation of reddened GI mucosa in 3 of 4 cats in the 0.3 mg/kg group and 1 of 4 cats in the 0.6 mg/kg group. All saline-treated cats were normal. By Day 9, one cat in both the 0.3 mg/kg group and the 0.6 mg/kg group died and another cat in the 0.3 mg/kg group was moribund. The cause of death for these cats could not be determined, although the pathologist reported pyloric/duodenal ulceration in the cats in 0.6 mg/kg group. The safety studies demonstrate a narrow margin of safety.

Injection Site Tolerance - Histopathology of the injection sites revealed hemorrhage and inflammation, myofiber atrophy, panniculitis, fibrin deposition, and fibroblast proliferation. These findings were present in cats in all groups, with the 3X cats having the most present. No safe repeat dose has been established in cats.

Storage Information: Store at controlled room temperature, 68-77°F (20-25°C). Use within 180 days of first puncture and puncture a maximum of 51 times.

How Supplied:
Loxicom 5 mg/mL Solution for Injection: 10 mL and 20 mL vial

Reference:

[1] Slingsby L.S., A.E. Waterman-Pearson. Comparison between meloxicam and carprofen for postoperative analgesia after feline ovariohysterectomy. Jour of Small Anim Pract (2002)43:286-289.

Made in the UK.
Norbrook Laboratories Limited,
Newry, BT35 6PU, Co. Down, Northern Ireland

Rev. 06/2021

Norbrook®

Approved by FDA under ANADA # 200-498

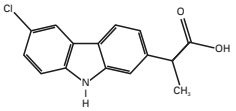
CARPRIEVE®
(carprofen tablets)
Caplets

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.

DESCRIPTION: Carprieve® (carprofen) is a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class that includes ibuprofen, naproxen, and ketoprofen. Carprofen is the nonproprietary designation for a substituted carbazole, 6-chloro-α-methyl-9H-carbazole-2-acetic acid.
The empirical formula is $C_{15}H_{12}ClNO_2$ and the molecular weight 273.72. The chemical structure of carprofen is:



Carprofen is a white, crystalline compound. It is freely soluble in ethanol, but practically insoluble in water at 25°C.

CLINICAL PHARMACOLOGY: Carprofen is a non-narcotic, non-steroidal anti-inflammatory agent with characteristic analgesic and antipyretic activity approximately equipotent to indomethacin in animal models.[1]

The mechanism of action of carprofen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity. Two unique cyclooxygenases have been described in mammals.[2] The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity. The specificity of a particular NSAID for COX-2 versus COX-1 may vary from species to species.[3] In an *in vitro* study using canine cell cultures, carprofen demonstrated selective inhibition of COX-2 versus COX-1.[4]

Clinical relevance of these data has not been shown. Carprofen has also been shown to inhibit the release of several prostaglandins in two inflammatory cell systems: rat polymorphonuclear leukocytes (PMN) and human rheumatoid synovial cells, indicating inhibition of acute (PMN system) and chronic (synovial cell system) inflammatory reactions.[1]

Several studies have demonstrated that carprofen has modulatory effects on both humoral and cellular immune responses.[5-9] Data also indicate that carprofen inhibits the production of osteoclast-activating factor (OAF), PGE_1, and PGE_2 by its inhibitory effects on prostaglandin biosynthesis.[1]

Based upon comparison with data obtained from intravenous administration, carprofen is rapidly and nearly completely absorbed (more than 90% bioavailable) when administered orally.[10] Peak blood plasma concentrations are achieved in 1-3 hours after oral administration of 1, 5, and 25 mg/kg to dogs. The mean terminal half-life of carprofen is approximately 8 hours (range 4.5-9.8 hours) after single oral doses varying from 1-35 mg/kg of body weight. After a 100 mg single intravenous bolus dose, the mean elimination half-life was approximately 11.7 hours in the dog. Carprofen is more than 99% bound to plasma protein and exhibits a very small volume of distribution.

Carprofen is eliminated in the dog primarily by biotransformation in the liver followed by rapid excretion of the resulting metabolites (the ester glucuronide of carprofen and the ether glucuronides of 2 phenolic metabolites, 7-hydroxy carprofen and 8-hydroxy carprofen) in the feces (70-80%) and urine (10-20%). Some enterohepatic circulation of the drug is observed.

INDICATIONS: Carprieve® is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

CONTRAINDICATIONS: Carprofen should not be used in dogs exhibiting previous hypersensitivity to carprofen.

WARNINGS:
Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans. **For use in dogs only.** Do not use in cats. Keep Carprieve in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

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

PRECAUTIONS: As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Effects may result from decreased prostaglandin production and inhibition of the enzyme cyclooxygenase which is responsible for the formation of prostaglandins from arachidonic acid.[11-14] When NSAIDs inhibit prostaglandins that cause inflammation they may also inhibit those prostaglandins which maintain normal homeostatic function. These anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease more often than in healthy patients.[12,14] NSAID therapy could unmask occult disease which has previously been undiagnosed due to the absence of apparent clinical signs. Patients with underlying renal disease for example, may experience exacerbation or decompensation of their renal disease while on NSAID therapy.[11-14] The use of parenteral fluids during surgery should be considered to reduce the potential risk of renal complications when using NSAIDs perioperatively.

Carprofen is an NSAID, and as with others in that class, adverse reactions may occur with its use. The most frequently reported effects have been gastrointestinal signs. Events involving suspected renal, hematologic, neurologic, dermatologic, and hepatic effects have also been reported. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be approached cautiously, with appropriate monitoring. Concomitant use of carprofen with other anti-inflammatory drugs, such as other NSAIDs or corticosteroids, should be avoided because of the potential increase of adverse reactions, including gastrointestinal ulcerations and/or perforations. Sensitivity to drug-associated adverse reactions varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Carprofen treatment was not associated with renal toxicity or gastrointestinal ulceration in well-controlled safety studies of up to ten times the dose in healthy dogs.

Carprieve® is not recommended for use in dogs with bleeding disorders (e.g., Von Willebrand's disease), as safety has not been established in dogs with these disorders. The safe use of Carprieve in animals less than 6 weeks of age, pregnant dogs, dogs used for breeding purposes, or in lactating bitches has not been established. Studies to determine the activity of carprofen when administered concomitantly with other protein-bound or similarly metabolized drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring additional therapy. Such drugs commonly used include cardiac, anticonvulsant and behavioral medications. It has been suggested that treatment with carprofen may reduce the level of inhalant anesthetics needed.[15]

If additional pain medication is warranted after administration of the total daily dose of Carprieve, alternative analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroid use to NSAID use.

INFORMATION FOR DOG OWNERS:
Carprieve, 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 decreased appetite, vomiting, diarrhea, 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 Carprieve 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.

ADVERSE REACTIONS:
During investigational studies of osteoarthritis with twice daily administration of 1 mg/lb, no clinically significant adverse reactions were reported. Some clinical signs were observed during field studies (n=297) which were similar for carprofen- and placebo-treated dogs. Incidences of the following were observed in both groups: vomiting (4%), diarrhea (4%), changes in appetite (3%), lethargy (1.4%), behavioral changes (1%), and constipation (0.3%). The product vehicle served as control.

There were no serious adverse events reported during clinical field studies of osteoarthritis with once daily administration of 2 mg/lb. The following categories of abnormal health observations were reported. The product vehicle served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Osteoarthritis Field Study (2 mg/lb once daily)

Observation	carprofen (n=129)	Placebo (n=132)
Inappetence	1.6	1.5
Vomiting	3.1	3.8
Diarrhea/Soft stool	3.1	4.5
Behavior change	0.8	0.8
Dermatitis	0.8	0.8
PU/PD	0.8	--
SAP increase	7.8	8.3
ALT increase	5.4	4.5
AST increase	2.3	0.8
BUN increase	3.1	1.5
Bilirubinuria	16.3	12.1
Ketonuria	14.7	9.1

Clinical pathology parameters listed represent reports of increases from pre-treatment values; medical judgment is necessary to determine clinical relevance.

During investigational studies of surgical pain for the caplet formulation, no clinically significant adverse reactions were reported. The product vehicle served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Surgical Pain Field Studies with Caplets (2 mg/lb once daily)

Observation* (n=148)	carprofen (n=149)	Placebo
Vomiting	10.1	13.4
Diarrhea/Soft stool	6.1	6.0
Ocular disease	2.7	0
Inappetence	1.4	0
Dermatitis/skin lesion	2.0	1.3
Dysrhythmia	0.7	0
Apnea	1.4	0
Oral/periodontal disease	1.4	0
Pyrexia	0.7	1.3
Urinary tract disease	1.4	1.3
Wound drainage	1.4	0

*A single dog may have experienced more than one occurrence of an event.

Post-Approval Experience:
Although not all adverse reactions are reported, the following adverse reactions are based on voluntary post-approval adverse drug experience reporting. The categories of adverse reactions are listed in decreasing order of frequency by body system.

Gastrointestinal: *Vomiting, diarrhea, constipation, inappetence, melena, hematemesis, gastrointestinal ulceration, gastrointestinal bleeding, pancreatitis.*

Hepatic: *Inappetence, vomiting, jaundice, acute hepatic toxicity, hepatic enzyme elevation, abnormal liver function test(s), hyperbilirubinemia, bilirubinuria, hypoalbuminemia. Approximately one-fourth of hepatic reports were in Labrador Retrievers.*

Neurologic: *Ataxia, paresis, paralysis, seizures, vestibular signs, disorientation.*

Urinary: *Hematuria, polyuria, polydipsia, urinary incontinence, urinary tract infection, azotemia, acute renal failure, tubular abnormalities including acute tubular necrosis, renal tubular acidosis, glucosuria.*

Behavioral: *Sedation, lethargy, hyperactivity, restlessness, aggressiveness.*

Hematologic: *Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, blood loss anemia, epistaxis.*

Dermatologic: *Pruritus, increased shedding, alopecia, pyotraumatic moist dermatitis (hot spots), necrotizing panniculitis/vasculitis, ventral ecchymosis.*

Immunologic or hypersensitivity: *Facial swelling, hives, erythema.*

In rare situations, death has been associated with some of the adverse reactions 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 http://www.fda.gov/reportanimalae

DOSAGE AND ADMINISTRATION: Always provide Client Information Sheet with prescription. Carefully consider the potential benefits and risk of CARPRIEVE and other treatment options before deciding to use CARPRIEVE. Use the lowest effective dose for the shortest duration consistent with individual response. The recommended dosage for oral administration to dogs is 2 mg/lb (4.4 mg/kg) of body weight daily. The total daily dose may be administered as 2 mg/lb of body weight once daily or divided and administered as 1 mg/lb (2.2 mg/kg) twice daily. For the control of postoperative pain, administer approximately 2 hours before the procedure. Caplets are scored and dosage should be calculated in half-caplet increments.

EFFECTIVENESS: Confirmation of the effectiveness of carprofen for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries, was demonstrated in 5 placebo-controlled, masked studies examining the anti-inflammatory and analgesic effectiveness of carprofen in various breeds of dogs.

Separate placebo-controlled, masked, multicenter field studies confirmed the anti-inflammatory and analgesic effectiveness of carprofen when dosed at 2 mg/lb once daily or when divided and administered at 1 mg/lb twice daily. In these two field studies, dogs diagnosed with osteoarthritis showed statistically significant overall improvement based on lameness evaluations by the veterinarian and owner observations when administered carprofen at labeled doses.

Separate placebo-controlled, masked, multicenter field studies confirmed the effectiveness of carprofen caplets for the control of postoperative pain when, dosed at 2 mg/lb once daily in various breeds of dogs. In these studies, dogs presented for ovariohysterectomy, cruciate repair and aural surgeries were administered carprofen preoperatively and for a maximum of 3 days (soft tissue) or 4 days (orthopedic) postoperatively. In general, dogs administered carprofen showed statistically significant improvement in pain scores compared to controls.

ANIMAL SAFETY: Laboratory studies in unanesthetized dogs and clinical field studies have demonstrated that carprofen is well tolerated in dogs after oral administration.
In target animal safety studies, carprofen was administered orally to healthy Beagle dogs at 1, 3, and 5 mg/lb twice daily (1, 3 and 5 times the recommended total daily dose) for 42 consecutive days with no significant adverse reactions. Serum albumin for a single female dog receiving 5 mg/lb twice daily decreased to 2.1 g/dL after 2 weeks of treatment, returned to the pre-treatment value (2.6 g/dL) after 4 weeks of treatment, and was 2.3 g/dL at the final 6-week evaluation. Over the 6-week treatment period, black or bloody stools were observed in 1 dog (1 incident) treated with 1 mg/lb twice daily and in 1 dog (2 incidents) treated with 3 mg/lb twice daily. Redness of the colonic mucosa was observed in 1 male that received 3 mg/lb twice daily.

Two of 8 dogs receiving 10 mg/lb orally twice daily (10 times the recommended total daily dose) for 14 days exhibited hypoalbuminemia. The mean albumin level in the dogs receiving this dose was lower (2.38 g/dL) than each of 2 placebo control groups (2.88 and 2.93 g/dL, respectively). Three incidents of black or bloody stool were observed in 1 dog. Five of 8 dogs exhibited reddened areas of duodenal mucosa on gross pathologic examination. Histologic examination of these areas revealed no evidence of ulceration, but did show minimal congestion of the lamina propria in 2 of the 5 dogs.

In separate safety studies lasting 13 and 52 weeks, respectively, dogs were administered orally up to11.4 mg/lb/day (5.7 times the recommended total daily dose of 2 mg/lb) of carprofen. In both studies, the drug was well tolerated clinically by all of the animals. No gross or histologic changes were seen in any of the treated animals. In both studies, dogs receiving the highest doses had average increases in serum L-alanine aminotransferase (ALT) of approximately 20 IU.

In the 52-week study, minor dermatologic changes occurred in dogs in each of the treatment groups but not in the control dogs. The changes were described as slight redness or rash and were diagnosed as non-specific dermatitis. The possibility exists that these mild lesions were treatment related, but no dose relationship was observed.

Clinical field studies were conducted with 549 dogs of different breeds at the recommended oral doses for 14 days (297 dogs were included in a study evaluating 1 mg/lb twice daily and 252 dogs were included in a separate study evaluating 2 mg/lb once daily). In both studies the drug was clinically well tolerated and the incidence of clinical adverse reactions for carprofen-treated animals was no higher than placebo-treated animals (placebo contained inactive ingredients found in carprofen). For animals receiving 1 mg/lb twice daily, the mean post-treatment serum ALT values were 11 IU greater and 9 IU less than pre-treatment values for dogs receiving carprofen and placebo, respectively. Differences were not statistically significant. For animals receiving 2 mg/lb once daily, the mean post-treatment serum ALT values were 4.5 IU greater and 0.9 IU less than pre-treatment values for dogs receiving carprofen and placebo, respectively. In the latter study, 3 carprofen-treated dogs developed a 3-fold or greater increase in (ALT) and/or (AST) during the course of therapy. One placebo-treated dog had a greater than 2-fold increase in ALT. None of these animals showed clinical signs associated with the laboratory value changes. Changes in clinical laboratory values (hematology and clinical chemistry) were not considered clinically significant. The 1 mg/lb twice daily course of therapy was repeated as needed at 2-week intervals in 244 dogs, some for as long as 5 years.

Clinical field studies were conducted in 297 dogs of different breeds undergoing orthopedic or soft tissue surgery. Dogs were administered 2 mg/lb of carprofen tablets two hours prior to surgery then once daily, as needed for 2 days (soft tissue surgery) or 3 days (orthopedic surgery). Carprofen was well tolerated when used in conjunction with a variety of anesthetic-related drugs. The type and severity of abnormal health observations in carprofen- and placebo-treated animals were approximately equal and few in number (see Adverse Reactions). The most frequent abnormal health observation was vomiting and was observed at approximately the same frequency in carprofen- and placebo-treated animals. Changes in clinicopathologic indices of hematopoietic, renal, hepatic, and clotting function were not clinically significant. The mean post-treatment serum ALT values were 7.3 IU and 2.5 IU less than pre-treatment values for dogs receiving carprofen and placebo, respectively. The mean post-treatment AST values were 3.1 IU less for dogs receiving carprofen and 0.2 IU greater for dogs receiving placebo.

STORAGE: Store at 59° to 86°F (15° to 30°C).
Use half-caplet within 30 days.

HOW SUPPLIED:
Carprieve caplets are scored, and contain 25 mg, 75 mg, or 100 mg of carprofen per caplet.
Each caplet size is packaged in bottles containing 30, 60, or 180 caplets.

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For a copy of the Safety Data Sheet (SDS) or to report adverse reactions call Norbrook at 1-866-591-5777.

Made in the UK.

Manufactured by:
Norbrook Laboratories Limited
Newry, BT35 6QQ, Co. Down,
Northern Ireland

TAKE TIME
OBSERVE LABEL DIRECTIONS

Norbrook®

Dog Owner Information about CARPRIEVE® (carprofen tablets) for Osteoarthritis and Post-Surgical Pain Generic name: carprofen ("car-prô-fen")

This summary contains important information about Carprieve®. You should read this information before you start giving your dog Carprieve and review it each time the 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 if you want to know more about Carprieve.

What is Carprieve?
Carprieve is a nonsteroidal anti-inflammatory drug (NSAID) that is used to reduce pain and inflammation (soreness) due to osteoarthritis and pain following surgery in dogs. Carprieve is a prescription drug for dogs. It is available as a caplet and chewable tablet and is given to dogs by mouth.

Osteoarthritis (OA) 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

To control surgical pain (e.g. for surgeries such as spays, ear procedures or orthopedic repairs) your veterinarian may administer Carprieve before the procedure and recommend that your dog be treated for several days after going home.

What kind of results can I expect when my dog is on Carprieve?
While Carprieve is not a cure for osteoarthritis, it can relieve the pain and inflammation of OA and improve your dog's mobility.
- Response varies from dog to dog but can be quite dramatic.
- In most dogs, improvement can be seen in a matter of days.
- If Carprieve is discontinued or not given as directed, your dog's pain and inflammation may come back.

Who should not take Carprieve?
Your dog should not be given Carprieve if he/she:
- Has had an allergic reaction to carprofen, the active ingredient of Carprieve.
- Has had an allergic reaction to aspirin or other NSAIDs (for example deracoxib, etodalac, firocoxib, meloxicam, phenylbutazone or tepoxalin) such as hives, facial swelling, or red or itchy skin.

Carprieve should be given to dogs only. Cats should not be given Carprieve. Call your veterinarian immediately if your cat receives Carprieve. People should not take Carprieve. Keep Carprieve and all medicines out of reach of children. Call your physician immediately if you accidentally take Carprieve.

How to give Carprieve to your dog.
Carprieve should be given according to your veterinarian's instructions. Your veterinarian will tell you what amount of Carprieve is right for your dog and for how long it should be given. Carprieve should be given by mouth and may be given with or without food.

What to tell/ask your veterinarian before giving Carprieve.
Talk to your veterinarian about:
- The signs of OA you have observed (for example limping, stiffness).
- The importance of weight control and exercise in the management of OA.
- What tests might be done before Carprieve is prescribed.
- How often your dog may need to be examined by your veterinarian.
- The risks and benefits of using Carprieve.

Tell your veterinarian if your dog has ever had the following medical problems:
- Experienced side effects from Carprieve or other NSAIDs, such as aspirin
- Digestive upset (vomiting and/or diarrhea)
- Liver disease
- Kidney disease
- A bleeding disorder (for example, Von Willebrand's disease)

Tell your veterinarian about:
- Any other medical problems or allergies that your dog has now or has had.
- All medicines that you are giving your dog or plan to give your dog, including those you can get without a prescription.

Tell your veterinarian if your dog is:
- Pregnant, nursing or if you plan to breed your dog.

What are the possible side effects that may occur in my dog during Carprieve therapy?
Carprieve, like other drugs, may cause some side effects. Serious but rare side effects have been reported in dogs taking NSAIDs, including Carprieve. Serious side effects can occur with or without warning and in rare situations result in death.

The most common NSAID-related side effects generally involve the stomach (such as bleeding ulcers), and liver or kidney problems. Look for the following side effects that can indicate your dog may be having a problem with Carprieve or may have another medical problem:
- 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, amount consumed)
- Change in urination habits (frequency, color, or smell)
- Change in skin (redness, scabs, or scratching)

It is important to stop therapy and contact your veterinarian immediately if you think your dog has a medical problem or side effect from Carprieve therapy. If you have additional questions about possible side effects, talk to your veterinarian.

Can Carprieve be given with other medicines?
Carprieve should not be given with other NSAIDs (for example aspirin, deracoxib, etodalac, firocoxib, meloxicam, tepoxalin) or steroids (for example cortisone, dexamethasone, prednisone, triamcinolone). Tell your veterinarian about all medicines you have given your dog in the past, and any medicines that you are planning to give with Carprieve. This should include other medicines that you can get without a prescription. 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 Carprieve?
Contact your veterinarian immediately if your dog eats more than the prescribed amount of Carprieve.

What else should I know about Carprieve?
This sheet provides a summary of information about Carprieve. If you have any questions or concerns about Carprieve, or osteoarthritis, or postoperative pain, talk to your veterinarian. As with all prescribed medicines, Carprieve should only be given to the dog for which it was prescribed. It should be given to your dog only for the condition for which it was prescribed.

It is important to periodically discuss your dog's response to Carprieve at regular check ups. Your veterinarian will best determine if your dog is responding as expected and if your dog should continue receiving Carprieve.

To report a suspected adverse reaction call Norbrook at 1-866-591-5777.
Made in the UK.
Manufactured by:
Norbrook Laboratories Limited
Newry, BT35 6QQ, Co. Down, Northern Ireland

L03 Rev Date: 04/2023

Approved by FDA under ANADA # 200-595

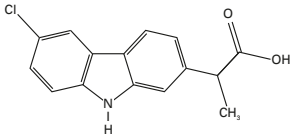
Carprieve® (carprofen)
Chewable Tablets

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.

DESCRIPTION: Carprieve® (carprofen) is a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class that includes ibuprofen, naproxen, and ketoprofen. Carprofen is the nonproprietary designation for a substituted carbazole, 6-chloro-α-methyl-9H-carbazole-2-acetic acid. The empirical formula is $C_{15}H_{12}ClNO_2$ and the molecular weight is 273.72. The chemical structure of carprofen is:



Carprofen is a white, crystalline compound. It is freely soluble in ethanol, but practically insoluble in water at 25°C.

CLINICAL PHARMACOLOGY: Carprofen is a non-narcotic, non-steroidal anti-inflammatory agent with characteristic analgesic and antipyretic activity approximately equipotent to indomethacin in animal models.[1]

The mechanism of action of carprofen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity. Two unique cyclooxygenases have been described in mammals.[2] The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity. The specificity of a particular NSAID for COX-2 versus COX-1 may vary from species to species.[3] In an *in vitro* study using canine cell cultures, carprofen demonstrated selective inhibition of COX-2 versus COX-1.[4]
Clinical relevance of these data has not been shown. Carprofen has also been shown to inhibit the release of several prostaglandins in two inflammatory cell systems: rat polymorphonuclear leukocytes (PMN) and human rheumatoid synovial cells, indicating inhibition of acute (PMN system) and chronic (synovial cell system) inflammatory reactions.[1]

Several studies have demonstrated that carprofen has modulatory effects on both humoral and cellular immune responses.[5-9] Data also indicate that carprofen inhibits the production of osteoclast-activating factor (OAF), PGE_1, and PGE_2 by its inhibitory effect in prostaglandin biosynthesis.[1]

Based upon comparison with data obtained from intravenous administration, carprofen is rapidly and nearly completely absorbed (more than 90% bioavailable) when administered orally.[10] Peak blood plasma concentrations are achieved in 1-3 hours after oral administration of 1, 5, and 25 mg/kg to dogs. The mean terminal half-life of carprofen is approximately 8 hours (range 4.5-9.8 hours) after single oral doses varying from 1-35 mg/kg of body weight. After a 100 mg single intravenous bolus dose, the mean elimination half-life was approximately 11.7 hours in the dog. Carprofen is more than 99% bound to plasma protein and exhibits a very small volume of distribution.

Carprofen is eliminated in the dog primarily by biotransformation in the liver followed by rapid excretion of the resulting metabolites (the ester glucuronide of carprofen and the ether glucuronides of 2 phenolic metabolites, 7-hydroxy carprofen and 8-hydroxy carprofen) in the feces (70-80%) and urine (10-20%). Some enterohepatic circulation of the drug is observed.

INDICATIONS: Carprieve is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

CONTRAINDICATIONS: Carprieve should not be used in dogs exhibiting previous hypersensitivity to carprofen.

WARNINGS: Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans. **For use in dogs only.** Do not use in cats.

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

PRECAUTIONS: As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal, and hepatic toxicity. Effects may result from decreased prostaglandin production and inhibition of the enzyme cyclooxygenase which is responsible for the formation of prostaglandins from arachidonic acid.[11-14] When NSAIDs inhibit prostaglandins that cause inflammation they may also inhibit those prostaglandins which maintain normal homeostatic function. These anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease more often than in healthy patients.[12,14]
NSAID therapy could unmask occult disease which has previously been undiagnosed due to the absence of apparent clinical signs. Patients with underlying renal disease for example, may experience exacerbation or decompensation of their renal disease while on NSAID therapy.[11-14] The use of parenteral fluids during surgery should be considered to reduce the potential risk of renal complications when using NSAIDs perioperatively.

Carprofen is an NSAID, and as with others in that class, adverse reactions may occur with its use. The most frequently reported effects have been gastrointestinal signs. Events involving suspected renal, hematologic, neurologic, dermatologic, and hepatic effects have also been reported. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be approached cautiously, with appropriate monitoring. Concomitant use of carprofen with other anti-inflammatory drugs, such as other NSAIDs or corticosteroids, should be avoided because of the potential increase of adverse reactions, including gastrointestinal ulcerations and/or perforations. Sensitivity to drug-associated adverse reactions varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Carprofen treatment was not associated with renal toxicity or gastrointestinal ulceration in well-controlled safety studies of up to ten times the dose in healthy dogs.

Carprieve is not recommended for use in dogs with bleeding disorders (e.g., Von Willebrand's disease), as safety has not been established in dogs with these disorders. The safe use of Carprieve in animals less than 6 weeks of age, pregnant dogs, dogs used for breeding purposes, or in lactating bitches has not been established. Studies to determine the activity of Carprieve when administered concomitantly with other protein-bound or similarly metabolized drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring additional therapy. Such drugs commonly used include cardiac, anticonvulsant and behavioral medications. It has been suggested that treatment with carprofen may reduce the level of inhalant anesthetics needed.[15]

If additional pain medication is warranted after administration of the total daily dose of Carprieve, alternative analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroids use to NSAID use.

Due to the liver flavoring contained in Carprieve chewable tablets, store out of the reach of dogs and in a secured area. Severe adverse reactions may occur if large quantities of tablets are ingested. If you suspect your dog has consumed Carprieve chewable tablets above the labeled dose, please call your veterinarian for immediate assistance and notify Norbrook (1-866-591-5777).

INFORMATION FOR DOG OWNERS:
Carprieve, 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 decreased appetite, vomiting, diarrhea, 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 Carprieve 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.

ADVERSE REACTIONS: During investigational studies for the caplet formulation with twice daily administration of 1 mg/lb, no clinically significant adverse reactions were reported. Some clinical signs were observed during field studies (n=297) which were similar for carprofen caplet- and placebo-treated dogs. Incidences of the following were observed in both groups: vomiting (4%), diarrhea (4%), changes in appetite (3%), lethargy (1.4%), behavioral changes (1%), and constipation (0.3%). The product vehicle served as control.

There were no serious adverse events reported during clinical field studies with once daily administration of 2 mg/lb.
The following categories of abnormal health observations were reported. The product vehicle served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Clinical Field Study (2 mg/lb once daily)

Observation	Carprofen (n=129)	Placebo (n=132)
Inappetence	1.6	1.5
Vomiting	3.1	3.8
Diarrhea/Soft stool	3.1	4.5
Behavior change	0.8	0.8
Dermatitis	0.8	0.8
PU/PD	0.8	--
SAP increase	7.8	8.3
ALT increase	5.4	4.5
AST increase	2.3	0.8
BUN increase	3.1	1.5
Bilirubinuria	16.3	12.1
Ketonuria	14.7	9.1

Clinical pathology parameters listed represent reports of increases from pre-treatment values; medical judgment is necessary to determine clinical relevance.
During investigational studies of surgical pain for the caplet formulation, no clinically significant adverse reactions were reported. The product vehicle served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Surgical Pain Field Studies with Caplets (2 mg/lb once daily)

Observation*	Carprofen (n=148)	Placebo (n=149)
Vomiting	10.1	13.4
Diarrhea/Soft stool	6.1	6.0
Ocular disease	2.7	0
Inappetence	1.4	0
Dermatitis/Skin lesion	2.0	1.3
Dysrhythmia	0.7	0
Apnea	1.4	0
Oral/Periodontal disease	1.4	0
Pyrexia	0.7	1.3
Urinary tract disease	1.4	1.3
Wound drainage	1.4	0

* A single dog may have experienced more than one occurrence of an event.

During investigational studies for the chewable tablet formulation, gastrointestinal signs were observed in some dogs. These signs included vomiting and soft stools.

Post-Approval Experience:
Although not all adverse reactions are reported, the following adverse reactions are based on voluntary post-approval adverse drug experience reporting. The categories of adverse reactions are listed in decreasing order of frequency by body system.

Gastrointestinal: *Vomiting, diarrhea, constipation, inappetence, melena, hematemesis, gastrointestinal ulceration, gastrointestinal bleeding, pancreatitis.*

Hepatic: *Inappetence, vomiting, jaundice, acute hepatic toxicity, hepatic enzyme elevation, abnormal liver function test(s), hyperbilirubinemia, bilirubinuria, hypoalbuminemia. Approximately one-fourth of hepatic reports were in Labrador Retrievers.*

Neurologic: *Ataxia, paresis, paralysis, seizures, vestibular signs, disorientation.*
Urinary: *Hematuria, polyuria, polydipsia, urinary incontinence, urinary tract infection, azotemia, acute renal failure, tubular abnormalities including acute tubular necrosis, renal tubular acidosis, glucosuria.*

Behavioral: *Sedation, lethargy, hyperactivity, restlessness, aggressiveness.*

Hematologic: *Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, blood loss anemia, epistaxis.*

Dermatologic: *Pruritus, increased shedding, alopecia, pyotraumatic moist dermatitis (hot spots), necrotizing panniculitis/vasculitis, ventral ecchymosis.*

Immunologic or hypersensitivity: *Facial swelling, hives, erythema.*

In rare situations, death has been associated with some of the adverse reactions listed above.

To report a suspected adverse reaction call 1-866-591-5777.

DOSAGE AND ADMINISTRATION: Always provide Client Information Sheet with prescription. Carefully consider the potential benefits and risk of Carprieve and other treatment options before deciding to use Carprieve. Use the lowest effective dose for the shortest duration consistent with individual response. The recommended dosage for oral administration to dogs is 2 mg/lb of body weight daily. The total daily dose may be administered as 2 mg/lb of body weight once daily or divided and administered as 1 mg/lb twice daily. For the control of postoperative pain, administer approximately 2 hours before the procedure. Carprieve chewable tablets are scored and dosage should be calculated in half-tablet increments. Tablets can be halved by placing the tablet on a hard surface and pressing down on both sides of the score. These liver flavored Carprieve chewable tablets may be offered to the dog by hand or placed on food. If the dog does not willingly consume the tablets, they may be hand-administered (pilled) as with other oral tablet medications. Care should be taken to ensure that the dog consumes the complete dose.

EFFECTIVENESS: Confirmation of the effectiveness of carprofen for the relief of pain and inflammation associated with osteoarthritis, and for the control of postoperative pain associated with soft tissue and orthopedic surgeries, was demonstrated in 5 placebo-controlled, masked studies examining the anti-inflammatory and analgesic effectiveness of carprofen caplets in various breeds of dogs.

Separate placebo-controlled, masked, multicenter field studies confirmed the anti-inflammatory and analgesic effectiveness of carprofen caplets when dosed at 2 mg/lb once daily or when divided and administered at 1 mg/lb twice daily. In these 2 field studies, dogs diagnosed with osteoarthritis showed statistically significant overall improvement based on lameness evaluations by the veterinarian and owner observations when administered carprofen at labeled doses.

Separate placebo-controlled, masked, multicenter-field studies confirmed the effectiveness of carprofen caplets for the control of postoperative pain when dosed at 2 mg/lb once daily in various breeds of dogs. In these studies, dogs presented for ovariohysterectomy, cruciate repair and aural surgeries were administered carprofen preoperatively and for a maximum of 3 days (soft tissue) or 4 days (orthopedic) postoperatively. In general, dogs administered carprofen showed statistically significant reduction in pain scores compared to controls.

ANIMAL SAFETY: Laboratory studies in unanesthetized dogs and clinical field studies have demonstrated that carprofen is well tolerated in dogs after oral administration. In target animal safety studies, carprofen was administered orally to healthy Beagle dogs at 1, 3, and 5 mg/lb twice daily (1, 3, and 5 times the recommended total daily dose) for 42 consecutive days with no significant adverse reactions.
Serum albumin for a single female dog receiving 5 mg/lb twice daily decreased to 2.1 g/dL after 2 weeks of treatment, returned to the pre-treatment value (2.6 g/dL) after 4 weeks of treatment, and was 2.3 g/dL at the final 6-week evaluation.
Over the 6-week treatment period, black or bloody stools were observed in 1 dog (1 incident) treated with 1 mg/lb twice daily and 1 dog (2 incidents) treated with 3 mg/lb twice daily. Redness of the colonic mucosa was observed in 1 male that received 3 mg/lb twice daily.

Two of 8 dogs receiving 10 mg/lb orally twice daily (10 times the recommended total daily dose) for 14 days exhibited hypoalbuminemia. The mean albumin level in the dogs receiving this dose was lower (2.38 g/dL) than each of two placebo control groups (2.88 and 2.93 g/dL, respectively). Three incidents of black or bloody stool were observed in 1 dog. Five of 8 dogs exhibited reddened areas of duodenal mucosa on gross pathologic examination. Histologic exam of these areas revealed no evidence of ulceration, but did show minimal congestion of the lamina propria in 2 of the 5 dogs.

In separate safety studies lasting 13 and 52 weeks, respectively, dogs were administered orally up to 11.4 mg/lb/day (5.7 times the recommended total daily dose of 2 mg/lb) of carprofen. In both studies, the drug was well tolerated clinically by all of the animals. No gross or histologic changes were seen in any of the treated animals. In both studies, dogs receiving the highest doses had average increases in serum L-alanine aminotransferase (ALT) of approximately 20 IU.

In the 52-week study, minor dermatologic changes occurred in dogs in each of the treatment groups but not in the control dogs. The changes were described as slight redness or rash and were diagnosed as non-specific dermatitis. The possibility exists that these mild lesions were treatment related, but no dose relationship was observed.

Clinical field studies were conducted with 549 dogs of different breeds at the recommended oral doses for 14 days (297 dogs were included in a study evaluating 1 mg/lb twice daily and 252 dogs were included in a separate study evaluating 2 mg/lb once daily). In both studies the drug was clinically well tolerated and the incidence of clinical adverse reactions for carprofen-treated animals was no higher than placebo-treated animals (placebo contained inactive ingredients found in carprofen caplets). For animals receiving 1mg/lb twice daily, the mean post-treatment serum ALT values were 11 IU greater and 9 IU less than pre-treatment values for dogs receiving carprofen and placebo, respectively. Differences were not statistically significant. For animals receiving 2 mg/lb once daily, the mean post-treatment serum ALT values were 4.5 IU greater and 0.9 IU less than pre-treatment values for dogs receiving carprofen and placebo, respectively. In the latter study, 3 carprofen-treated dogs developed a 3-fold or greater increase in (ALT) and/or (AST) during the course of therapy. One placebo-treated dog had a greater than 2-fold increase in ALT. None of these animals showed clinical signs associated with laboratory value changes. Changes in the clinical laboratory values (hematology and clinical chemistry) were not considered clinically significant. The 1 mg/lb twice daily course of therapy was repeated as needed at 2-week intervals in 244 dogs, some for as long as 5 years.

Clinical field studies were conducted in 297 dogs of different breeds undergoing orthopedic or soft tissue surgery. Dogs were administered 2 mg/lb of carprofen two hours prior to surgery then once daily, as needed for 2 days (soft tissue surgery) or 3 days (orthopedic surgery). Carprofen was well tolerated when used in conjunction with a variety of anesthetic-related drugs. The type and severity of abnormal health observation in carprofen- and placebo-treated animals were approximately equal and few in number (see Adverse Reactions). The most frequent abnormal health observation was vomiting and was observed at approximately the same frequency in carprofen- and placebo-treated animals. Changes in clinicopathologic indices of hematopoietic, renal, hepatic, and clotting function were not clinically significant. The mean post-treatment serum ALT values were 7.3 IU and 2.5 IU less than pre-treatment values for dogs receiving carprofen and placebo respectively. The mean post-treatment AST values were 3.1 IU less for dogs receiving carprofen and 0.2 IU greater for dogs receiving placebo.

STORAGE: Store at controlled room temperature, 68-77°F (20-25°C); excursions permitted 15-30°C (59-86°F). Use half-tablet within 30 days.

HOW SUPPLIED: Carprieve chewable tablets are scored, and contain 25 mg, 75 mg, or 100 mg of carprofen per tablet. Each tablet size is packaged in bottles containing 30, 60, or 180 tablets.

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For a copy of the Safety Data Sheet (SDS) or to report adverse reactions call Norbrook at 1-866-591-5777.
Made in the UK.

Manufactured by:
Norbrook Laboratories Limited, Newry, BT35 6PU, Co. Down, Northern Ireland

I02 December 2021

TAKE TIME
OBSERVE LABEL DIRECTIONS

Norbrook®

Dog Owner Information about Carprieve® (carprofen)

Chewable Tablets

for Osteoarthritis and Post-Surgical Pain

Generic name: carprofen ("car-prō-fen")

This summary contains important information about Carprieve®. You should read this information before you start giving your dog Carprieve and review it each time the 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 if you want to know more about Carprieve.

What is Carprieve?
Carprieve is a nonsteroidal anti-inflammatory drug (NSAID) that is used to reduce pain and inflammation (soreness) due to osteoarthritis and pain following surgery in dogs. Carprieve is a prescription drug for dogs. It is available as a caplet and chewable tablet and is given to dogs by mouth.

Osteoarthritis (OA) 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

To control surgical pain (e.g. for surgeries such as spays, ear procedures or orthopedic repairs) your veterinarian may administer Carprieve before the procedure and recommend that your dog be treated for several days after going home.

What kind of results can I expect when my dog is on Carprieve?
While Carprieve is not a cure for osteoarthritis, it can relieve the pain and inflammation of OA and improve your dog's mobility.
- Response varies from dog to dog but can be quite dramatic.
- In most dogs, improvement can be seen in a matter of days.
- If Carprieve is discontinued or not given as directed, your dog's pain and inflammation may come back.

Who should not take Carprieve?
Your dog should not be given Carprieve if he/she:
- Has had an allergic reaction to carprofen, the active ingredient of Carprieve.
- Has had an allergic reaction to aspirin or other NSAIDs (for example deracoxib, etodolac, firocoxib, meloxicam, phenylbutazone or tepoxalin) such as hives, facial swelling, or red or itchy skin.

Carprieve should be given to dogs only. Cats should not be given Carprieve. Call your veterinarian immediately if your cat receives Carprieve. People should not take Carprieve. Keep Carprieve and all medicines out of reach of children. Call your physician immediately if you accidentally take Carprieve.

How to give Carprieve to your dog.
Carprieve should be given according to your veterinarian's instructions. Your veterinarian will tell you what amount of Carprieve is right for your dog and how long it should be given. Offer Carprieve chewable tablets to the dog by hand or place in the dog's mouth. If the dog does not willingly consume the tablet, hand-administer (pill). Carprieve may be given with or without food.

What to tell/ask your veterinarian before giving Carprieve.
Talk to your veterinarian about:
- The signs of OA you have observed (for example limping, stiffness).
- The importance of weight control and exercise in the management of OA.
- What tests might be done before Carprieve is prescribed.
- How often your dog may need to be examined by your veterinarian.
- The risks and benefits of using Carprieve.

Tell your veterinarian if your dog has ever had the following medical problems:
- Experienced side effects from Carprieve or other NSAIDs such as aspirin
- Digestive upset (vomiting and/or diarrhea)
- Liver disease
- Kidney disease
- A bleeding disorder (for example, Von Willebrand's disease)

Tell your veterinarian about:
- Any other medical problems or allergies that your dog has now or has had.
- All medicines that you are giving your dog or plan to give your dog, including those you can get without a prescription.

Tell your veterinarian if your dog is:
- Pregnant, nursing or if you plan to breed your dog.

What are the possible side effects that may occur in my dog during Carprieve therapy?
Carprieve, like other drugs, may cause some side effects. Serious but rare side effects have been reported in dogs taking NSAIDs, including Carprieve. Serious side effects can occur with or without warning and in rare situations result in death.
The most common NSAID-related side effects generally involve the stomach (such as bleeding ulcers), and liver or kidney problems. Look for the following side effects that can indicate your dog may be having a problem with Carprieve or may have another medical problem:
- 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, amount consumed)
- Change in urination habits (frequency, color, or smell)
- Change in skin (redness, scabs, or scratching)

It is important to stop therapy and contact your veterinarian immediately if you think your dog has a medical problem or side effect from Carprieve therapy. If you have additional questions about possible side effects, talk to your veterinarian.

Can Carprieve be given with other medicines?
Carprieve should not be given with other NSAIDs (for example, aspirin, deracoxib, etodolac, firocoxib, meloxicam, tepoxalin) or steroids (for example, cortisone, dexamethasone, prednisone, triamcinolone).

Tell your veterinarian about all medicines you have given your dog in the past, and any medicines that you are planning to give with Carprieve. This should include other medicines that you can get without a prescription. 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 Carprieve?
Contact your veterinarian immediately if your dog eats more than the prescribed amount of Carprieve.

How to store Carprieve Chewable Tablets.
Carprieve Chewable Tablets are designed to taste good to animals.
Keep Carprieve Chewable Tablets in a secured storage area out of the reach of your dog and other pets. If your dog ingests more than your veterinarian prescribed, or if your other pets take Carprieve Chewable Tablets, contact your veterinarian right away.

What else should I know about Carprieve?
This sheet provides a summary of information about Carprieve. If you have any questions or concerns about Carprieve or osteoarthritis pain, or postoperative pain, talk to your veterinarian.

As with all prescribed medicines, Carprieve should only be given to the dog for which it was prescribed. It should be given to your dog only for the condition for which it was prescribed.
It is important to periodically discuss your dog's response to Carprieve at regular check ups. Your veterinarian will best determine if your dog is responding as expected and if your dog should continue receiving Carprieve.
To report a suspected adverse reaction call Norbrook at 1-866-591-5777.

Made in the UK.

Manufactured by:
Norbrook Laboratories Limited
Newry, BT35 6PU, Co. Down, Northern Ireland

I02 December 2021

Norbrook®

Approved by FDA under ANADA # 200-520

Carprieve® Injection (carprofen)

Sterile Injectable Solution

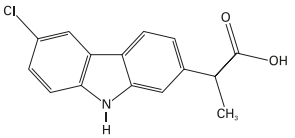
50 mg/mL

Non-steroidal anti-inflammatory drug

For subcutaneous use in dogs only

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

DESCRIPTION: Carprieve® Injection is a sterile solution containing carprofen, a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class that includes ibuprofen, naproxen, and ketoprofen. Carprofen is the non-proprietary designation for a substituted carbazole, 6-chloro-α-methyl-9H-carbazole-2-acetic acid. The empirical formula is $C_{15}H_{12}ClNO_2$ and the molecular weight 273.72. The chemical structure of carprofen is:



Each mL of Carprieve Injection contains 50.0 mg carprofen, 30.0 mg arginine, 88.5 mg glycocholic acid, 169.0 mg lecithin, 10.0 mg benzyl alcohol, 6.17 mg sodium hydroxide, with additional sodium hydroxide and hydrochloric acid as needed to adjust pH, and water for injection.

CLINICAL PHARMACOLOGY: Carprofen is a non-narcotic, non-steroidal anti-inflammatory agent with characteristic analgesic and antipyretic activity approximately equipotent to indomethacin in animal models.[1]

The mechanism of action of carprofen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity. Two unique cyclooxygenases have been described in mammals.[2] The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity. The specificity of a particular NSAID for COX-2 versus COX-1 may vary from species to species.[3] In an *in vitro* study using canine cell cultures, carprofen demonstrated selective inhibition of COX-2 versus COX-1.[4] Clinical relevance of these data has not been shown. Carprofen has also been shown to inhibit the release of several prostaglandins in two inflammatory cell systems: rat polymorphonuclear leukocytes (PMN) and human rheumatoid synovial cells, indicating inhibition of acute (PMN system) and chronic (synovial cell system) inflammatory reactions.[1]

Several studies have demonstrated that carprofen has modulatory effects on both humoral and cellular immune responses.[5-9] Data also indicate that carprofen inhibits the production of osteoclast-activating factor (OAF), PGE_1, and PGE_2 by its inhibitory effects on prostaglandin biosynthesis.[1]

Based upon comparison with data obtained from intravenous administration, carprofen is rapidly and nearly completely absorbed (more than 90% bioavailable) when administered orally.[10] Peak blood plasma concentrations are achieved in 1-3 hours after oral administration of 1, 5, and 25 mg/kg to dogs. The mean terminal half-life of carprofen is approximately 8 hours (range 4.5-9.8 hours) after single oral doses varying from 1-35 mg/kg of body weight. After a 100 mg single intravenous bolus dose, the mean elimination half-life was approximately 11.7 hours in the dog. Carprofen is more than 99% bound to plasma protein and exhibits a very small volume of distribution.

Comparison of a single 25 mg dose in Beagle dogs after subcutaneous and oral administration demonstrated that the dorsoscapular subcutaneous administration results in a slower rate of drug input (as reflected by mean peak observed concentrations) but comparable total drug absorption within a 12 hour dosing interval (as reflected by area under the curve from hours zero to 12 postdose).

Carprofen is eliminated in the dog primarily by biotransformation in the liver followed by rapid excretion of the resulting metabolites (the ester glucuronide of carprofen and the ether glucuronides of 2 phenolic metabolites, 7-hydroxy carprofen and 8-hydroxy carprofen) in the feces (70-80%) and urine (10-20%). Some enterohepatic circulation of the drug is observed.

INDICATIONS: Carprieve Injection is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

CONTRAINDICATIONS: Carprofen should not be used in dogs exhibiting previous hypersensitivity to carprofen.

WARNINGS:
Keep out of reach of children. Not for human use. Consult a physician in cases of accidental human exposure. **For use in dogs only.** Do not use in cats.

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

PRECAUTIONS: As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Effects may result from decreased prostaglandin production and inhibition of the enzyme cyclooxygenase which is responsible for the formation of prostaglandins from arachidonic acid.[11-14] When NSAIDs inhibit prostaglandins that cause inflammation they may also inhibit those prostaglandins which maintain normal homeostatic function. These anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease more often than in healthy patients.[12,14] NSAID therapy could unmask occult disease which has previously been undiagnosed due to the absence of apparent clinical signs. Patients with underlying renal disease for example, may experience exacerbation or decompensation of their renal disease while on NSAID therapy.[11-14] The use of parenteral fluids during surgery should be considered to reduce the potential risk of renal complications when using NSAIDs perioperatively.

Carprofen is an NSAID, and as with others in that class, adverse reactions may occur with its use. The most frequently reported effects have been gastrointestinal signs. Events involving suspected renal, hematologic, neurologic, dermatologic, and hepatic effects have also been reported. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be approached cautiously, with appropriate monitoring. Concomitant use of carprofen with other anti-inflammatory drugs, such as other NSAIDs or corticosteroids, should be avoided because of the potential increase of adverse reactions, including gastrointestinal ulcerations and/or perforations. Sensitivity to drug-associated adverse reactions varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Carprofen treatment was not associated with renal toxicity or gastrointestinal ulceration in well-controlled safety studies of up to ten times the dose in healthy dogs. As with any parenterally injected product, good hygienic procedures should be used when administering Carprieve Injection. It is suggested to use different sites for additional injections.

Carprieve Injection is not recommended for use in dogs with bleeding disorders (e.g., Von Willebrand's disease), as safety has not been established in dogs with these disorders. The safe use of Carprieve Injection in animals less than 6 weeks of age, pregnant dogs, dogs used for breeding purposes, or in lactating bitches has not been established. Safety has not been established for IV or IM administration. Studies to determine the activity of carprofen when administered concomitantly with other protein-bound or similarly metabolized drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring additional therapy. Such drugs commonly used include cardiac, anticonvulsant and behavioral medications. It has been suggested that treatment with carprofen may reduce the level of inhalant anesthetics needed.[15] If additional pain medication is warranted after administration of the total daily dose of carprofen, alternative analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroid use to NSAID use.

INFORMATION FOR DOG OWNERS: Carprieve Injection, 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 decreased appetite, vomiting, diarrhea, 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 Carprieve Injection 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.

ADVERSE REACTIONS: During investigational studies for the caplet formulation, no clinically significant adverse reactions were reported. Some clinical signs were observed during field studies (n=297) which were similar for carprofen- and placebo-treated dogs. Incidences of the following were observed in both groups: vomiting (4%), diarrhea (4%), changes in appetite (3%), lethargy (1.4%), behavioral changes (1 %), and constipation (0.3%). The product vehicle served as control.

There were no serious adverse events reported during clinical field studies with once daily oral administration of 2 mg/lb. The following categories of abnormal health observations were reported. The product vehicle served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Clinical Field Study (2 mg/lb once daily)

Observation	carprofen caplet (n=129)	Placebo (n=132)
Inappetence	1.6	1.5
Vomiting	3.1	3.8
Diarrhea/Soft stool	3.1	4.5
Behavior change	0.8	0.8
Dermatitis	0.8	0.8
PU/PD	0.8	--
SAP increase	7.8	8.3
ALT increase	5.4	4.5
AST increase	2.3	0.8
BUN increase	3.1	1.5
Bilirubinuria	16.3	12.1
Ketonuria	14.7	9.1

Clinical pathology parameters listed represent reports of increases from pre-treatment values; the use of clinical judgment is necessary to determine clinical relevance (refers also to table below). There were no serious adverse events reported during clinical field studies for the injectable formulation. The following categories of abnormal health observations were reported. Saline served as placebo control.

Percentage of Dogs with Abnormal Health Observations Reported in Clinical Field Studies with the Injectable

Observation*	carprofen (n=168)	Placebo (n=163)
Vomiting	10.1	9.2
Diarrhea/Soft stool	2.4	3.7
Dermatitis	0.6	1.2
Dysrhythmia	0.6	0.6
Swelling	0	1.2
Dehiscence	1.2	0
WBC increase	13.7	6.7

*A single dog may have experienced more than one occurrence of an event.

Post-Approval Experience:
Although not all adverse reactions are reported, the following adverse reactions are based on voluntary post-approval adverse drug experience reporting. The categories of adverse reactions are listed by body system.

Gastrointestinal: *Vomiting, diarrhea, constipation, inappetence, melena, hematemesis, gastrointestinal ulceration, gastrointestinal bleeding, pancreatitis.*

Hepatic: *Inappetence, vomiting, jaundice, acute hepatic toxicity, hepatic enzyme elevation, abnormal liver function test(s), hyperbilirubinemia, bilirubinuria, hypoalbuminemia. Approximately one-fourth of hepatic reports were in Labrador Retrievers.*

Neurologic: *Ataxia, paresis, paralysis, seizures, vestibular signs, disorientation.*

Urinary: *Hematuria, polyuria, polydipsia, urinary incontinence, urinary tract infection, azotemia, acute tubular necrosis, renal tubular acidosis, glucosuria.*

Behavioral: *Sedation, lethargy, hyperactivity, restlessness, aggressiveness.*

Hematologic: *Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, blood loss anemia, epistaxis.*

Dermatologic: *Pruritus, increased shedding, alopecia, pyotraumatic moist dermatitis (hot spots), necrotizing panniculitis/vasculitis, ventral ecchymosis. In rare situations, injection site reactions including necrosis, abscess and seroma formation, and granulomas have been reported with the injectable formulation.*

Immunologic or hypersensitivity: *Facial swelling, hives, erythema.*

In rare situations, death has been associated with some of the adverse reactions 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 http://www.fda.gov/reportanimalae

DOSAGE AND ADMINISTRATION: Carefully consider the potential benefits and risks of carprofen and other treatment options before deciding to use Carprieve Injection. Use the lowest effective dose for the shortest duration consistent with individual response. The recommended dosage for subcutaneous administration to dogs is 2 mg/lb (4.4 mg/kg) of body weight daily. The total daily dose may be administered as either 2 mg/lb of body weight once daily or divided and administered as 1 mg/lb (2.2 mg/kg) twice daily. For control of postoperative pain, administer approximately 2 hours before the procedure.

EFFECTIVENESS: Confirmation of the effectiveness of carprofen for the relief of pain and inflammation associated with osteoarthritis, and for the control of postoperative pain associated with soft tissue and orthopedic surgeries was demonstrated in 7 placebo-controlled, masked studies examining the anti-inflammatory and analgesic effectiveness of carprofen caplets and injectable in various breeds of dogs.

Separate placebo-controlled, masked, multicenter field studies confirmed the anti-inflammatory and analgesic effectiveness of carprofen caplets when dosed at 2 mg/lb once daily or when divided and administered at 1 mg/lb twice daily. In these two field studies, dogs diagnosed with osteoarthritis showed statistically significant overall improvement based on lameness evaluations by the veterinarian and owner observations when administered carprofen at labeled doses.

Based upon the blood level comparison between subcutaneous and oral administration, carprofen effectiveness for osteoarthritis after dorsoscapular subcutaneous and oral administration should be similar, although there may be a slight delay in the onset of relief after subcutaneous injection.

Separate placebo-controlled, masked, multicenter field studies confirmed the effectiveness of carprofen injectable for the control of postoperative pain when dosed at 2 mg/lb once daily in various breeds of dogs. In these studies, dogs presented for ovariohysterectomy, cruciate repair and aural surgeries were administered carprofen preoperatively and for a maximum of 3 days (soft tissue) or 4 days (orthopedic) postoperatively. In general, dogs administered carprofen showed statistically significant improvement in pain scores compared to controls.

ANIMAL SAFETY: Laboratory studies in unanesthetized dogs and clinical field studies have demonstrated that carprofen is well tolerated in dogs after oral and subcutaneous administration.

In target animal safety studies, carprofen was administered orally to healthy Beagle dogs at 1, 3, and 5 mg/lb twice daily (1, 3 and 5 times the recommended total daily dose) for 42 consecutive days with no significant adverse reactions. Serum albumin for a single female dog receiving 5 mg/lb twice daily decreased to 2.1 g/dL after 2 weeks of treatment, returned to the pre-treatment value (2.6 g/dL) after 4 weeks of treatment, and was 2.3 g/dL at the final 6-week evaluation. Over the 6-week treatment period, black or bloody stools were observed in 1 dog (1 incident) treated with 1 mg/lb twice daily and in 1 dog (2 incidents) treated with 3 mg/lb twice daily. Redness of the colonic mucosa was observed in 1 male that received 3 mg/lb twice daily.

Two of 8 dogs receiving 10 mg/lb orally twice daily (10 times the recommended total daily dose) for 14 days exhibited hypoalbuminemia. The mean albumin level in the dogs receiving this dose was lower (2.38 g/dL) than each of 2 placebo control groups (2.88 and 2.93 g/dL, respectively). Three incidents of black or bloody stool were observed in 1 dog. Five of 8 dogs exhibited reddened areas of duodenal mucosa on gross pathologic examination. Histologic examination of these areas revealed no evidence of ulceration, but did show minimal congestion of the lamina propria in 2 of the 5 dogs.

In separate safety studies lasting 13 and 52 weeks, respectively, dogs were administered orally up to 11.4 mg/lb/day (5.7 times the recommended total daily dose of 2 mg/lb) of carprofen. In both studies, the drug was well tolerated clinically by all of the animals. No gross or histologic changes were seen in any of the treated animals. In both studies, dogs receiving the highest doses had average increases in serum L-alanine aminotransferase (ALT) of approximately 20 IU.

In the 52-week study, minor dermatologic changes occurred in dogs in each of the treatment groups but not in the control dogs. The changes were described as slight redness or rash and were diagnosed as non-specific dermatitis. The possibility exists that these mild lesions were treatment related, but no dose relationship was observed.

Clinical field studies were conducted with 549 dogs of different breeds at the recommended oral doses for 14 days (297 dogs were included in a study evaluating 1 mg/lb twice daily and 252 dogs were included in a separate study evaluating 2 mg/lb once daily). In both studies the drug was clinically well tolerated and the incidence of clinical adverse reactions for carprofen-treated animals was no higher than placebo-treated animals (placebo contained inactive ingredients found in carprofen caplets). For animals receiving 1 mg/lb twice daily, the mean post-treatment serum ALT values were 11 IU greater and 9 IU less than pretreatment values for dogs receiving carprofen caplets and placebo, respectively. Differences were not statistically significant. For animals receiving 2 mg/lb once daily, the mean post-treatment serum ALT values were 4.5 IU greater and 0.9 IU less than pre-treatment values for dogs receiving carprofen caplets and placebo, respectively. In the latter study, 3 carprofen-treated dogs developed a 3-fold or greater increase in (ALT) and/or (AST) during the course of therapy. One placebo-treated dog had a greater than 2-fold increase in ALT. None of these animals showed clinical signs associated with the laboratory value changes. Changes in clinical laboratory values (hematology and clinical chemistry) were not considered clinically significant.

The 1 mg/lb twice daily course of therapy was repeated as needed at 2-week intervals in 244 dogs, some for as long as 5 years.

Clinical field studies were conducted on 331 dogs undergoing orthopedic or soft tissue surgery. Dogs were administered 2 mg/lb of carprofen subcutaneously two hours prior to surgery and once daily thereafter, as needed, for 2 days (soft tissue surgery) or 3 days (orthopedic surgery). Carprofen was well tolerated when used in conjunction with a variety of anesthetic-related drugs. The type and severity of abnormal health observations in carprofen- and placebo-treated animals were approximately equal and few in number (see Adverse Reactions). The most frequent abnormal health observation was vomiting and was observed at approximately the same frequency in carprofen- and placebo-treated animals. Changes in clinicopathologic indices of hematopoetic, renal, hepatic, and clotting function were not clinically significant. The mean post-treatment serum ALT values were 8.4 IU and 7.0 IU less than pre-treatment values for dogs receiving carprofen and placebo, respectively. The mean post-treatment AST values were 1.5 IU and 0.7 IU greater for dogs receiving carprofen and placebo, respectively.

Swelling and warmth were associated with the injection site after subcutaneous administration of carprofen injectable. These findings were not clinically significant. Long term use of the injectable has not been studied.

STORAGE: Store under refrigeration at 36° to 46°F (2° to 8°C). Once broached, product may be stored at temperatures up to 77°F (25°C). Use within 56 days of first puncture.

HOW SUPPLIED: Carprieve Injection is supplied in 20 mL and 50 mL, amber, glass, sterile, multi-dose vials.

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Norbrook Laboratories Limited
Newry, BT35 6QQ, Co. Down,
Northern Ireland

TAKE TIME
OBSERVE LABEL DIRECTIONS

Rev. December 2022 120670I03

Norbrook®

Approved by FDA under ANADA # 200-720

Enroflox® Chewable Tablets (enrofloxacin)

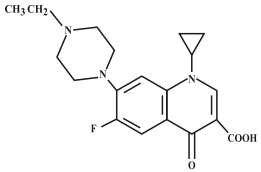
Antibacterial Tablets For Dogs And Cats

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

▶ Federal law prohibits the extralabel use of this drug in food-producing animals. ◀

DESCRIPTION
Enrofloxacin is a synthetic chemotherapeutic agent from the class of the quinolone carboxylic acid derivatives. It has antibacterial activity against a broad spectrum of Gram negative and Gram positive bacteria (See Tables I and II). It is rapidly absorbed from the digestive tract, penetrating into all measured body tissues and fluids (See Table III).
Tablets are available in three sizes (22.7, 68.0 and 136.0 mg enrofloxacin).

CHEMICAL NOMENCLATURE AND STRUCTURAL FORMULA:
1-cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.



ACTIONS:
Microbiology: Quinolone carboxylic acid derivatives are classified as DNA gyrase inhibitors. The mechanism of action of these compounds is very complex and not yet fully understood. The site of action is bacterial gyrase, a synthesis promoting enzyme. The effect on *Escherichia coli* is the inhibition of DNA synthesis through prevention of DNA supercoiling. Among other things, such compounds lead to the cessation of cell respiration and division. They may also interrupt bacterial membrane integrity.[1]

Enrofloxacin is bactericidal, with activity against both Gram negative and Gram positive bacteria. The minimum inhibitory concentrations (MICs) were determined for a series of 39 isolates representing 9 genera of bacteria from natural infections in dogs and cats, selected principally because of resistance to one or more of the following antibiotics: ampicillin, cephalothin, colistin, chloramphenicol, erythromycin, gentamicin, kanamycin, penicillin, streptomycin, tetracycline, triple sulfa and sulfa/trimethoprim. The MIC values for enrofloxacin against these isolates are presented in Table I.
Most strains of these organisms were found to be susceptible to enrofloxacin *in vitro* but the clinical significance has not been determined for some of the isolates.

The susceptibility of organisms to enrofloxacin should be determined using enrofloxacin 5 mcg disks.
Specimens for susceptibility testing should be collected prior to the initiation of enrofloxacin therapy.

TABLE I — MIC Values for Enrofloxacin Against Canine and Feline Pathogens (Diagnostic laboratory isolates , 1984)

Organisms	Isolates	MIC Range (mcg/mL)
Bacteroides spp.	2	2
Bordetella bronchiseptica	3	0.125-0.5
Brucella canis	2	0.125-0.25
Clostridium perfringens	1	0.5
Escherichia coli	5*	≤0.016-0.031
Klebsiella spp.	11*	0.031-0.5
Proteus mirabilis	6	0.062-0.125
Pseudomonas aeruginosa	4	0.5-8
Staphylococcus spp.	5	0.125

*Includes feline isolates
The inhibitory activity on 120 isolates of seven canine urinary pathogens was also investigated and is listed in Table II.

TABLE II — MIC Values for Enrofloxacin Against Canine Urinary Pathogens (Diagnostic laboratory isolates , 1985)

Organisms	Isolates	MIC Range (mcg/mL)
E. coli	30	0.06-2.0
P. mirabilis	20	0.125-2.0
K. pneumoniae	20	0.06-0.5
P. aeruginosa	10	1.0-8.0
Enterobacter spp.	10	0.06-1.0
Staph. (coag. +)	20	0.125-0.5
Strep. (alpha hemol.)	10	0.5-8.0

Distribution in the Body: Enrofloxacin penetrates into all canine and feline tissues and body fluids. Concentrations of drug equal to or greater than the MIC for many pathogens (See Tables I, II and III) are reached in most tissues by two hours after dosing at 2.5 mg/kg and are maintained for 8-12 hours after dosing. Particularly high levels of enrofloxacin are found in urine. A summary of the body fluid/tissue drug levels at 2 to 12 hours after dosing at 2.5 mg/kg is given in Table III.

Table III — Body Fluid/Tissue distribution of Enrofloxacin in Dogs and Cats Single Oral Dose = 2.5 mg/kg (1.13 mg/lb)

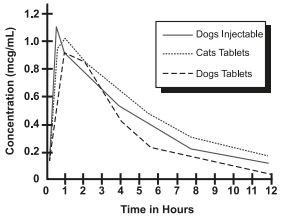
	Post-treatment Enrofloxacin Levels			
	Canine (n = 2)		Feline (n = 4)	
Body Fluids (mcg/mL)	**2 Hr.**	**8 Hr.**	**2 Hr.**	**12 Hr.**
Bile	–	–	2.13	1.97
Cerebrospinal Fluid	–	–	0.37	0.10
Urine	43.05	55.35	12.81	26.41
Eye Fluids	0.53	0.66	0.45	0.65
Whole Blood	1.01	0.36	–	–
Plasma	0.67	0.33	–	–
Serum	–	–	0.48	0.18
Tissues (mcg/g) Hematopoietic System				
Liver	3.02	1.36	1.84	0.37
Spleen	1.45	0.85	1.33	0.52
Bone Marrow	2.10	1.22	1.68	0.64
Lymph Node	1.32	0.91	0.49	0.21
Urogenital System				
Kidney	1.87	0.99	1.43	0.37
Bladder Wall	1.36	0.98	1.16	0.55
Testes	1.36	1.10	1.01	0.28
Prostate	1.36	2.20	1.88	0.55
Ovaries	–	–	0.78	0.56
Uterine Wall	1.59	0.29	0.81	1.05
Gastrointestinal and Cardiopulmonary Systems				
Lung	1.34	0.82	0.91	0.33
Heart	1.88	0.78	0.84	0.32
Stomach	3.24	2.16	3.26	0.27
Small Intestine	2.10	1.11	2.72	0.40
Large Intestine	–	–	0.94	1.10
Other				
Fat	0.52	0.40	0.24	0.11
Skin	0.66	0.48	0.46	0.17
Muscle	1.62	0.77	0.53	0.29
Brain	0.25	0.24	0.22	0.12
Mammary Gland	0.45	0.21	0.36	0.30
Feces	1.65	9.97	0.37	4.18

Pharmacokinetics: In dogs, the absorption and elimination characteristics of the oral formulation are linear (plasma concentrations increase proportionally with dose) when enrofloxacin is administered at up to 11.5 mg/kg, twice daily[2]. Approximately 80% of the orally administered dose enters the systemic circulation unchanged. The eliminating organs, based on the drug's body clearance time, can readily remove the drug with no indication that the eliminating mechanisms are saturated. The primary route of excretion is via the urine. The absorption and elimination characteristics beyond this point are unknown. In cats, no oral absorption information is available at other than 2.5 mg/kg, administered orally as a single dose. Saturable absorption and/or elimination processes may occur at greater doses. When saturation of the absorption process occurs, the plasma concentration of the active moiety will be less than predicted, based on the concept of dose proportionality.

Following an oral dose in dogs of 2.5 mg/kg (1.13 mg/lb), enrofloxacin reached 50% of its maximum serum concentration in 15 minutes and peak serum level was reached in one hour. The elimination half-life in dogs is approximately 2.5 - 3 hours at that dose, while in cats it is greater than 4 hours. In a study comparing dogs and cats, the peak concentration and the time to peak concentration were not different.

A graph indicating the mean serum levels following a dose of 2.5 mg/kg (1.13 mg/lb) in dogs (oral and intramuscular) and cats (oral) is shown in Figure 1.

Figure 1 - Serum Concentrations of Enrofloxacin Following a Single Oral or Intramuscular Dose at 2.5 mg /kg in Dogs and a Single Oral Dose at 2.5 mg /kg in Cats.



Breakpoint: Based on pharmacokinetic studies of enrofloxacin in dogs and cats after a single oral administration of 2.5 mg enrofloxacin/kg BW (i.e. half of the lowest-end single daily dose range for dogs and half the single daily dose for cats) and the data listed in Tables I and II, the following breakpoints are recommended for canine and feline isolates.

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 21	≤ 0.5	Susceptible (S)
18 - 20	1	Intermediate (I)
≤ 17	≥ 2	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable plasma levels. A report of "Intermediate" is a technical buffer and isolates falling into this category should be retested. Alternatively the organism may be successfully treated if the infection is in a body site where drug is physiologically concentrated. A report of "Resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms for both standardized disk diffusion assays and standardized dilution assays. The 5 µg enrofloxacin disk should give the following zone diameters and enrofloxacin powder should provide the following MIC values for reference strains.

QC strain	MIC (µg/mL)	Zone Diameter (mm)
E. coli ATCC 25922	0.008 - 0.03	32 - 40
P. aeruginosa ATCC 27853	1 - 4	15 - 19
S. aureus ATCC 25923		27 - 31
S. aureus ATCC 29213	0.03 - 0.12	

INDICATIONS:
Enroflox® Chewable Tablets (enrofloxacin) are indicated for the management of diseases associated with bacteria susceptible to enrofloxacin. Enroflox Chewable Tablets are indicated for use in dogs and cats.

EFFICACY CONFIRMATION:
Dogs : Clinical efficacy was established in dermal infections (wounds and abscesses) associated with susceptible strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Staphylococcus intermedius*; respiratory infections (pneumonia, tonsillitis, rhinitis) associated with susceptible strains of *Escherichia coli* and *Staphylococcus aureus*; and urinary cystitis associated with susceptible strains of *Escherichia coli*, *Proteus mirabilis*, and *Staphylococcus aureus*.

Cats : Clinical efficacy was established in dermal infections (wounds and abscesses) associated with susceptible strains of *Pasteurella multocida*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*.

CONTRAINDICATIONS:
Enrofloxacin is contraindicated in dogs and cats known to be hypersensitive to quinolones.
Dogs : Based on the studies discussed under the section on Animal Safety Summary, the use of enrofloxacin is contraindicated in small and medium breeds of dogs during the rapid growth phase (between 2 and 8 months of age). The safe use of enrofloxacin has not been established in large and giant breeds during the rapid growth phase.
Large breeds may be in this phase for up to one year of age and the giant breeds for up to 18 months. In clinical field trials utilizing a daily oral dose of 5.0 mg/kg, there were no reports of lameness or joint problems in any breed. However, controlled studies with histological examination of the articular cartilage have not been conducted in the large or giant breeds.

ADVERSE REACTIONS:
Dogs : Two of the 270 (0.7%) dogs treated with enrofloxacin tablets at 5.0 mg/kg per day in the clinical field studies exhibited side effects, which were apparently drug-related. These two cases of vomition were self-limiting.
Post-Approval Experience: The following adverse experiences, although rare, are based on voluntary post-approval adverse drug experience reporting. The categories of reactions are listed in decreasing order of frequency by body system.
Gastrointestinal: anorexia, diarrhea, vomiting, elevated liver enzymes
Neurologic: ataxia, seizures
Behavioral: depression, lethargy, nervousness
Cats : No drug-related side effects were reported in 124 cats treated with enrofloxacin tablets at 5.0 mg/kg per day for 10 days in clinical field studies.
Post-Approval Experience: The following adverse experiences, although rare, are based on voluntary post-approval adverse drug experience reporting. The categories of reactions are listed in decreasing order of frequency by body system.
Ocular: Mydriasis, retinal degeneration (retinal atrophy, attenuated retinal vessels, and hyperreflective tapeta have been reported), loss of vision. Mydriasis may be an indication of impending or existing retinal changes.
Gastrointestinal: vomiting, anorexia, elevated liver enzymes, diarrhea
Neurologic: ataxia, seizures
Behavioral: depression, lethargy, vocalization, aggression
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.

ANIMAL SAFETY SUMMARY:
Dogs : Adult dogs receiving enrofloxacin orally at a daily dosage rate of 52 mg/kg for 13 weeks had only isolated incidences of vomition and inappetence. Adult dogs receiving the tablet formulation for 30 consecutive days at a daily treatment of 25 mg/kg did not exhibit significant clinical signs nor were there effects upon the clinical chemistry, hematological or histological parameters. Daily doses of 125 mg/kg for up to 11 days induced vomition, inappetence, depression, difficult locomotion and death while adult dogs receiving 50 mg/kg/day for 14 days had clinical signs of vomition and inappetence.

Adult dogs dosed intramuscularly for three treatments at 12.5 mg/kg followed by 57 oral treatments at 12.5 mg/kg, all at 12 hour intervals, did not exhibit either significant clinical signs or effects upon the clinical chemistry, hematological or histological parameters.

Oral treatment of 15 to 28 week old growing puppies with daily dosage rates of 25 mg/kg has induced abnormal carriage of the carpal joint and weakness in the hindquarters. Significant improvement of clinical signs is observed following drug withdrawal. Microscopic studies have identified lesions of the articular cartilage following 30 day treatments at either 5, 15 or 25 mg/kg in this age group. Clinical signs of difficult ambulation or associated cartilage lesions have not been observed in 29 to 34 week old puppies following daily treatments of 25 mg/kg for 30 consecutive days nor in 2 week old puppies with the same treatment schedule.

Tests indicated no effect on circulating microfilariae or adult heartworms (*Dirofilaria immitis*) when dogs were treated at a daily dosage rate of 15 mg/kg for 30 days. No effect on cholinesterase values was observed.

No adverse effects were observed on reproductive parameters when male dogs received 10 consecutive daily treatments of 15 mg/kg/day at 3 intervals (90, 45 and 14 days) prior to breeding or when female dogs received 10 consecutive daily treatments of 15 mg/kg/day at 4 intervals: between 30 and 0 days prior to breeding, early pregnancy (between 10th & 30th days), late pregnancy (between 40th & 60th days), and during lactation (the first 28 days).
Cats : Cats in age ranges of 3 to 4 months and 7 to 10 months received daily treatments of 25 mg/kg for 30 consecutive days with no adverse effects upon the clinical chemistry, hematological or histological parameters. In cats 7-10 months of age treated daily for 30 consecutive days, 2 of 4 receiving 5 mg/kg, 3 of 4 receiving 15 mg/kg, 2 of 4 receiving 25 mg/kg and 1 of 4 nontreated controls experienced occasional vomition. Five to 7 month old cats had no side effects with daily treatments of 15 mg/kg for 30 days, but 2 of 4 animals had articular cartilage lesions when administered 25 mg/kg per day for 30 days.

Doses of 125 mg/kg for 5 consecutive days to adult cats induced vomition, depression, incoordination and death while those receiving 50 mg/kg for 6 days had clinical signs of vomition, inappetence, incoordination and convulsions, but they returned to normal.

Enrofloxacin was administered to thirty-two (8 per group), six- to eight-month-old cats at doses of 0, 5, 20, and 50 mg/kg of body weight once a day for 21 consecutive days. There were no adverse effects observed in cats that received 5 mg/kg body weight of enrofloxacin. The administration of enrofloxacin at 20 mg/kg body weight or greater caused salivation, vomition, and depression. Additionally, dosing at 20 mg/kg body weight or greater resulted in mild to severe fundic lesions on ophthalmologic examination (change in color of the fundus, central or generalized retinal degeneration), abnormal electroretinograms (including blindness), and diffuse light microscopic changes in the retina.

DRUG INTERACTIONS:
Compounds that contain metal cations (e.g., aluminum, calcium, iron, magnesium) may reduce the absorption of some quinolone-class drugs from the intestinal tract. Concomitant therapy with other drugs that are metabolized in the liver may reduce the clearance rates of the quinolone and the other drug.
Dogs : Enrofloxacin has been administered to dogs at a daily dosage rate of 10 mg/kg concurrently with a wide variety of other health products including anthelmintics (praziquantel, febantel, sodium disophenol), insecticides (fenthion, pyrethrins), heartworm preventatives (diethylcarbamazine) and other antibiotics (ampicillin, gentamicin sulfate, penicillin, dihydrostreptomycin). No incompatibilities with other drugs are known at this time.
Cats : Enrofloxacin was administered at a daily dosage rate of 5 mg/kg concurrently with anthelmintics (praziquantel, febantel), an insecticide (propoxur) and another antibacterial (ampicillin). No incompatibilities with other drugs are known at this time.

WARNINGS:
For use in animals only. In rare instances, use of this product in cats has been associated with Retinal Toxicity. Do not exceed 5 mg/kg of body weight per day in cats. Safety in breeding or pregnant cats has not been established. Keep out of reach of children.

Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposure. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight.

For customer service or to obtain product information, including Safety Data Sheet (SDS), call 1-866-591-5777.

PRECAUTIONS:
Quinolone-class drugs should be used with caution in animals with known or suspected Central Nervous System (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation which may lead to convulsive seizures.

Quinolone-class drugs have been associated with cartilage erosions in weight-bearing joints and other forms of arthropathy in immature animals of various species.

The use of fluoroquinolones in cats has been reported to adversely affect the retina. Such products should be used with caution in cats.

DOSAGE AND ADMINISTRATION:
Dogs : Administer orally at a rate to provide 5-20 mg/kg (2.27 to 9.07 mg/lb) of body weight. Selection of a dose within the range should be based on clinical experience, the severity of disease, and susceptibility of the pathogen. Animals which receive doses in the upper-end of the dose range should be carefully monitored for clinical signs that may include inappetence, depression, and vomition.

Weight of Dog	**Once Daily Dosing Chart**			
	5.0 mg/kg	10.0 mg/kg	15.0 mg/kg	20.0 mg/kg
9.1 kg (20 lb)	2 x 22.7 mg tablets	1 x 22.7 mg plus 1 x 68 mg tablets	1 x 136 mg tablet	1 x 136 mg plus 2 x 22.7 mg tablets
27.2 kg (60 lb)	1 x 136 mg tablet	2 x 136 mg tablets	3 x 136 mg tablets	4 x 136 mg tablets

All tablet sizes are double scored for accurate dosing.

Cats : Administer orally at 5 mg/kg (2.27 mg/lb) of body weight. The dose for dogs and cats may be administered either as a single daily dose or divided into two (2) equal daily doses administered at twelve (12) hour intervals. The dose should be continued for at least 2-3 days beyond cessation of clinical signs, to a maximum of 30 days.

Weight of Cat	**Once Daily Dosing Chart (5 mg/kg/day)**
5 lb (2.27 kg)	1/2 x 22.7 mg tablet
10 lb (4.5 kg)	1 x 22.7 mg tablet
15 lb (6.8 kg)	1 and 1/2 x 22.7 mg tablets or 1/2 x 68 mg tablet

All tablet sizes are double scored for accurate dosing.

Dogs & Cats: The duration of treatment should be selected based on clinical evidence. Generally, administration of Enroflox Chewable Tablets (enrofloxacin) should continue for at least 2-3 days beyond cessation of clinical signs. For severe and/or complicated infections, more prolonged therapy, up to 30 days, may be required. If no improvement is seen within five days, the diagnosis should be reevaluated and a different course of therapy considered.

The lower limit of the dose range in dogs and the daily dose for cats was based on efficacy studies in dogs and cats where enrofloxacin was administered at 2.5 mg/kg twice daily. Target animal safety and toxicology were used to establish the upper limit of the dose range for dogs and treatment duration for dogs and cats.

STORAGE:
Dispense tablets in tight containers only. Enroflox Chewable Tablets (enrofloxacin) should be stored at or below 77° F (25°C). Use half and quarter tablets within 90 days.

HOW SUPPLIED:

Tablet Size	**Tablets /Bottle**	**Tablet Size**	**Tablets /Bottle**
22.7 mg	50 Double Scored	68.0 mg	200 Double Scored
22.7 mg	200 Double Scored	136.0 mg	50 Double Scored
68.0 mg	50 Double Scored	136.0 mg	200 Double Scored

Norbrook, the Norbrook bull and Enroflox® are registered trademarks of Norbrook Laboratories Limited.

REFERENCES:
1. Doughherty, T.J., & Saukkonen, J.J. (1985). Membrane permeability changes associated with DNA gyrase inhibitors in Escherichia Coli. Antimicrob Agents Chemother, 28 (2), 200-206.
2. Walker, R.D., Stein, G.E., Hauptmam, J.G., McDonald, K.H. (1992). Pharmacokinetic evaluation of enrofloxacin administered orally to healthy dogs. Am J Vet Res, 53 (12):2315-2319.

Norbrook Laboratories Limited
Newry, Co. Down, BT35 6PU, Northern Ireland
Made in the UK

December 2021

Norbrook®

Approved by FDA under ANADA # 200-513

Enroflox®
(enrofloxacin)
Injection For Dogs
2.27%

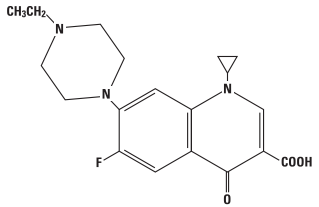
For Dogs Only

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

Federal law prohibits the extralabel use of this drug in food-producing animals.

DESCRIPTION:
Enrofloxacin is a synthetic chemotherapeutic agent from the class of the quinolone carboxylic acid derivatives. It has antibacterial activity against a broad spectrum of Gram negative and Gram positive bacteria (See Tables I and II). Each mL of injectable solution contains: enrofloxacin 22.7 mg, n-butyl alcohol 30 mg, potassium hydroxide for pH adjustment and water for injection, q.s.

CHEMICAL NOMENCLATURE AND STRUCTURAL FORMULA:
1-cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1, 4-dihydro-4-oxo-3-quinolinecarboxylic acid.



ACTIONS:
Microbiology: Quinolone carboxylic acid derivatives are classified as DNA gyrase inhibitors. The mechanism of action of these compounds is very complex and not yet fully understood. The site of action is bacterial gyrase, a synthesis promoting enzyme. The effect of *Escherichia coli* is the inhibition of DNA synthesis through prevention of DNA supercoiling. Among other things, such compounds lead to the cessation of cell respiration and division. They may also interrupt bacterial membrane integrity.[1]

Enrofloxacin is bactericidal, with activity against both Gram negative and Gram positive bacteria. The minimum inhibitory concentrations (MICs) were determined for a series of 37 isolates representing 9 genera of bacteria from natural infections in dogs, selected principally because of resistance to one or more of the following antibiotics: ampicillin, cephalothin, colistin, chloramphenicol, erythromycin, gentamicin, kanamycin, penicillin, streptomycin, tetracycline, triple sulfa and sulfa/trimethoprim. The MIC values for enrofloxacin against these isolates are presented in Table I. Most strains of these organisms were found to be susceptible to enrofloxacin *in vitro* but the clinical significance has not been determined for some of the isolates.

The susceptibility of organisms to enrofloxacin should be determined using enrofloxacin 5 mcg disks. Specimens for susceptibility testing should be collected prior to the initiation of enrofloxacin therapy.

TABLE I – MIC Values for Enrofloxacin Against Canine Pathogens (Diagnostic laboratory isolates, 1984)

Organisms	Isolates	MIC Range (mcg/mL)
Bacteroides spp.	2	2
Bordatella bronchiseptica	3	0.125-0.5
Brucella canis	2	0.125-0.25
Clostridium perfringens	1	0.5
Escherichia coli	4	≤0.016-0.031
Klebsiella spp.	10	0.031-0.5
Proteus mirabilis	6	0.062-0.125
Pseudomonas aeruginosa	4	0.5-8
Staphylococcus spp.	5	0.125

The inhibitory activity on 120 isolates of seven canine urinary pathogens was also investigated and is listed in Table II.

TABLE II – MIC Values for Enrofloxacin Against Canine Urinary Pathogens (Diagnostic laboratory isolates, 1985)

Organisms	Isolates	MIC Range (mcg/mL)
E. coli	30	0.06-2.0
P. mirabilis	20	0.125-2.0
K. pneumoniae	20	0.06-0.5
P. aeruginosa	10	1.0-8.0
Enterobacter spp.	10	0.06-1.0
Staph. (coag. +)	20	0.125-0.5
Strep. (alpa hemol.)	10	0.5-8.0

Distribution in the Body: Enrofloxacin penetrates into all canine tissues and body fluids. Concentrations of drug equal to or greater than the MIC for many pathogens (See Tables I, II and III) are reached in most tissues by two hours after dosing at 2.5 mg/kg and are maintained for 8-12 hours after dosing. Particularly high levels of enrofloxacin are found in urine.
A summary of the body fluid/tissue drug levels at 2 to 12 hours after dosing at 2.5 mg/kg is given in Table III.

TABLE III – Body Fluid/Tissue distribution of Enrofloxacin in Dogs
Single Oral Dose = 2.5 mg/kg (1.13 mg/lb)
Post-treatment Enrofloxacin Levels Canine (n=2)

Body Fluids (mcg/mL)	2 Hr.	8 Hr.
Urine	43.05	55.35
Eye Fluids	0.53	0.66
Whole Blood	1.01	0.36
Plasma	0.67	0.33
Tissues (mcg/g) Hematopoietic System		
Liver	3.02	1.36
Spleen	1.45	0.85
Bone Marrow	2.10	1.22
Lymph Node	1.32	0.91
Urogenital System		
Kidney	1.87	0.99
Bladder Wall	1.36	0.98
Testes	1.36	1.10
Prostate	1.36	2.20
Uterine Wall	1.59	0.29
Gastrointestinal and Cardiopulmonary Systems		
Lung	1.34	0.82
Heart	1.88	0.78
Stomach	3.24	2.16
Small Intestine	2.10	1.11
Other		
Fat	0.52	0.40
Skin	0.66	0.48
Muscle	1.62	0.77
Brain	0.25	0.24
Mammary Gland	0.45	0.21
Feces	1.65	9.97

Pharmacokinetics: In dogs, the absorption and elimination characteristics of the oral formulation are linear (plasma concentrations increase proportionally with dose) when enrofloxacin is administered at up to 11.5 mg/kg, twice daily.[2] Approximately 80% of the orally administered dose enters the systemic circulation unchanged. The eliminating organs, based on the drug's body clearance time, can readily remove the drug with no indication that the eliminating mechanisms are saturated. The primary route of excretion is via the urine. The absorption and elimination characteristics beyond this point are unknown. Saturable absorption and/or elimination processes may occur at greater doses. When saturation of the absorption process occurs, the plasma concentration of the active moiety will be less than predicted, based on the concept of dose proportionality.

Following an oral dose in dogs of 2.5 mg/kg (1.13 mg/lb), enrofloxacin reached 50% of its maximum serum concentration in 15 minutes and peak serum level was reached in one hour. The elimination half-life in dogs is approximately 2 ½ -3 hours at that dose.

A graph indicating the mean serum levels following a dose of 2.5 mg/kg (1.13 mg/lb) in dogs (oral and intramuscular) is shown in Figure I.

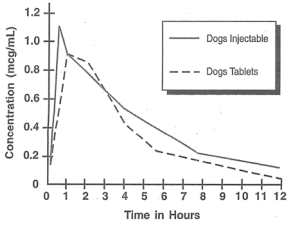


Figure 1 – Serum Concentrations of Enrofloxacin Following a Single Oral or Intramuscular Dose at 2.5 mg/kg in Dogs.

Breakpoint: Based on pharmacokinetic studies of enrofloxacin in dogs after a single oral administration of 2.5 mg enrofloxacin/kg BW (i.e. half of the lowest-end single daily dose range) and the data listed in Tables I and II, the following breakpoints are recommended for canine isolates.

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 21	≤ 0.5	Susceptible (S)
18-20	1	Intermediate (I)
≤ 17	≥ 2	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable plasma levels. A report of "Intermediate" is a technical buffer and isolates falling into this category should be retested. Alternatively the organism may be successfully treated if the infection is in a body site where drug is physiologically concentrated. A report of "Resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected.
Standardized procedures require the use of laboratory control organisms for both standardized disk diffusion assays and standardized dilution assays. The 5 µg enrofloxacin disk should give the following zone diameters and enrofloxacin powder should provide the following MIC values for reference strains.

QC Strain	MIC (µg/mL)	Zone Diameter (mm)
E. coli ATCC 25922	0.008 - 0.03	32 - 40
P. aeruginosa ATCC 27853	1 - 4	15 - 19
S. aureus ATCC 25923		27 - 31
S. aureus ATCC 29213	0.03 - 0.12	

INDICATIONS:
Enroflox® (brand of enrofloxacin) Injectable Solution is indicated for the management of diseases in dogs associated with bacteria susceptible to enrofloxacin.

EFFICACY CONFIRMATION:
Clinical efficacy was established in dermal infections (wounds and abscesses) associated with susceptible strains of *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* and *Staphylococcus intermedius;* respiratory infections (pneumonia, tonsillitis, rhinitis) associated with susceptible strains of *Escherichia coli* and *Staphylococcus aureus* and urinary cystitis associated with susceptible strains of *Escherichia coli, Proteus mirabilis,* and *Staphylococcus aureus.*

CONTRAINDICATIONS:
Enrofloxacin is contraindicated in dogs known to be hypersensitive to quinolones.

Based on the studies discussed under the section on Animal Safety Summary, the use of enrofloxacin is contraindicated in small and medium breeds of dogs during the rapid growth phase (between 2 and 8 months of age). The safe use of enrofloxacin has not been established in large and giant breeds during the rapid growth phase. Large breeds may be in this phase for up to one year of age and the giant breeds for up to 18 months. In clinical field trials utilizing a daily oral dose of 5.0 mg/kg, there were no reports of lameness or joint problems in any breed. However, controlled studies with histological examination of the articular cartilage have not been conducted in the large or giant breeds.

ADVERSE REACTIONS:
No drug-related side effects were reported in 122 clinical cases treated with an enrofloxacin injectable solution followed by enrofloxacin tablets at 5.0 mg/kg per day.
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.

ANIMAL SAFETY SUMMARY:
Adult dogs receiving enrofloxacin orally at a daily dosage rate of 52 mg/kg for 13 weeks had only isolated incidences of vomition and inappetence. Adult dogs receiving the tablet formulation for 30 consecutive days at a daily treatment of 25 mg/kg did not exhibit significant clinical signs nor were there effects upon the clinical chemistry, hematological or histological parameters. Daily doses of 125 mg/kg for up to 11 days induced vomition, inappetence, depression, difficult locomotion and death while adult dogs receiving 50 mg/kg/day for 14 days had clinical signs of vomition and inappetence.

Adult dogs dosed intramuscularly for three treatments at 12.5 mg/kg followed by 57 oral treatments at 12.5 mg/kg, all at 12 hour intervals, did not exhibit either significant clinical signs or effects upon the clinical chemistry, hematological or histological parameters.

Oral treatment of 15 to 28 week old growing puppies with daily dosage rates of 25 mg/kg has induced abnormal carriage of the carpal joint and weakness in the hindquarters. Significant improvement of clinical signs is observed following drug withdrawal. Microscopic studies have identified lesions of the articular cartilage following 30 day treatments at either 5, 15 or 25 mg/kg in this age group. Clinical signs of difficult ambulation or associated cartilage lesions have not been observed in 29 to 34 week old puppies following daily treatments of 25 mg/kg for 30 consecutive days nor in 2 week old puppies with the same treatment schedule.

Tests indicated no effect on circulating microfilariae or adult heartworms *(Dirofilaria immitis)* when dogs were treated at a daily dosage rate of 15 mg/kg for 30 days. No effect on cholinesterase values was observed.

No adverse effects were observed on reproductive parameters when male dogs received 10 consecutive daily treatments of 15 mg/kg/day at 3 intervals (90, 45 and 14 days) prior to breeding or when female dogs received 10 consecutive daily treatments of 15 mg/kg/day at 4 intervals; between 30 and 0 days prior to breeding, early pregnancy (between 10th and 30th days), late pregnancy (between 40th and 60th days), and during lactation (the first 28 days).

DRUG INTERACTIONS:
Concomitant therapy with other drugs that are metabolized in the liver may reduce the clearance rates of the quinolone and the other drug.

Enrofloxacin has been administered to dogs at a daily dosage rate of 10 mg/kg concurrently with a wide variety of other health products including anthelmintics (praziquantel, febantel), insecticides (pyrethrins), heartworm preventatives (diethylcarbamazine) and other antibiotics (ampicillin, gentamicin sulfate, penicillin). No incompatibilities are known with other drugs at this time.

WARNINGS:
For use in animals only. The use of this product in cats may result in Retinal Toxicity. Keep out of reach of children.
Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposure. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight.
For customer service, to obtain a copy of the Safety Data Sheet (SDS) or to report adverse reactions call Norbrook at 1-866-591-5777.

PRECAUTION:
Quinolone-class drugs should be used with caution in animals with known or suspected Central Nervous System (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation which may lead to convulsive seizures.

Quinolone-class drugs have been associated with cartilage erosions in weight-bearing joints and other forms of arthropathy in immature animals of various species.

The use of fluoroquinolones in cats has been reported to adversely affect the retina. Such products should be used with caution in cats.

DOSAGE AND ADMINISTRATION:
Enroflox Injection for Dogs may be used as the initial dose at 2.5 mg/kg. It should be administered intramuscularly (IM) as a single dose, followed by initiation of enrofloxacin tablet therapy.

Enroflox Injection for Dogs may be administered as follows:

Weight Of Animal	**Enroflox® Injection for Dogs* 2.5 mg/kg**
9.1 kg (20 lb)	1.00 mL
27.2 kg (60 lb)	3.00 mL

*The initial Enroflox Injection for Dogs administration should be followed 12 hours later by initiation of enrofloxacin tablet therapy.

The lower limit of the dose range was based on efficacy studies in dogs where enrofloxacin was administered at 2.5 mg/kg twice daily. Target animal safety and toxicology studies were used to establish the upper limit of the dose range and treatment duration.

STORAGE:
Store at 59°-77°F (15°-25°C). Excursions permitted up to 86°F (30°C). Brief exposure to temperature up to 104°F (40°C) may be tolerated provided the mean kinetic temperature does not exceed 77°F (25°C); however, such exposure should be minimized. Protect from direct sunlight. Do not freeze. Use within 90 days of first puncture.

HOW SUPPLIED:
Enroflox Injection for Dogs Vial Sizes 20 mL, 50 mL and 100 mL

REFERENCES:
[1] Dougherty, T.J. and Saukkonen, J.J. Membrane Permeability Changes Associated with DNA Gyrase Inhibitors in *Escherichia coli.* Antimicrob. Agents and Chemoth., V. 28, Aug. 1985: 200-206.

[2] Walker, R.D., *et al.* Pharmacokinetic Evaluation of Enrofloxacin Administered Orally to Healthy Dogs. Am.J.Res., V. 53, No. 12, Dec. 1992: 2315-2319.

Made in the UK.

Norbrook Laboratories Limited
Newry, BT35 6QQ, Co. Down,
Northern Ireland

TAKE TIME
OBSERVE LABEL DIRECTIONS

Rev. 06/22

Norbrook®

04767I004

Selarid®
(selamectin)

Topical Parasiticide For Dogs and Cats

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

DESCRIPTION:
Selarid® (selamectin) Topical Parasiticide is available as a colorless to yellow, ready to use solution in single dose applicators for topical (dermal) treatment of dogs six weeks of age and older and cats eight weeks of age and older. The content of each applicator is formulated to provide a minimum of 2.7 mg/lb (6 mg/kg) of body weight of selamectin. The chemical composition of selamectin is (5Z,25S)-25-cyclohexyl-4'-*O*-de (2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)-5-demethoxy -25-de(1-methylpropyl)-22,23-dihydro-5-hydroxyiminoavermectin A_{1a}.

INDICATIONS:
Selarid is recommended for use in dogs six weeks of age or older and cats eight weeks of age and older for the following parasites and indications:

Dogs:
Selarid kills adult fleas and prevents flea eggs from hatching for one month and is indicated for the prevention and control of flea infestations (*Ctenocephalides felis*), prevention of heartworm disease caused by *Dirofilaria immitis*, and the treatment and control of ear mite (*Otodectes cynotis*) infestations. Selarid also is indicated for the treatment and control of sarcoptic mange (*Sarcoptes scabiei*) and for the control of tick infestations due to *Dermacentor variabilis*.

Cats:
Selarid kills adult fleas and prevents flea eggs from hatching for one month and is indicated for the prevention and control of flea infestations (*Ctenocephalides felis*), prevention of heartworm disease caused by *Dirofilaria immitis*, and the treatment and control of ear mite (*Otodectes cynotis*) infestations. Selarid is also indicated for the treatment and control of roundworm (*Toxocara cati*) and intestinal hookworm (*Ancylostoma tubaeforme*) infections in cats.

DOSAGE AND ADMINISTRATION:
The recommended minimum dose is 2.7 mg selamectin per pound (6 mg/kg) of body weight.

Administer the entire contents of a single dose applicator (or two applicators used in combination for dogs weighing over 130 pounds) of Selarid topically in accordance with the following tables.

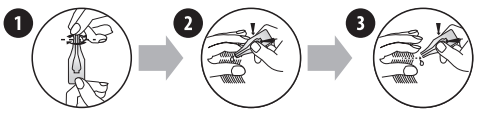
Cats (lb)	Package color	mg per applicator	Potency (mg/mL)	Administered volume (mL)
Up to 5	Mauve	15 mg	60	0.25
5.1 – 15	Blue	45 mg	60	0.75
15.1 - 22	Taupe	60 mg	60	1.0

For cats over 22 lbs use the appropriate combination of applicators

Dogs (lb)	Package color	mg per applicator	Potency (mg/mL)	Administered volume (mL)
Up to 5	Mauve	15 mg	60	0.25
5.1 – 10	Purple	30 mg	120	0.25
10.1 – 20	Brown	60 mg	120	0.5
20.1 – 40	Red	120 mg	120	1.0
40.1 – 85	Teal	240 mg	120	2.0
85.1 - 130	Plum	360 mg	120	3.0

For dogs over 130 lbs use the appropriate combination of applicators. Recommended for use in dogs 6 weeks of age and older and in cats 8 weeks of age and older.

A veterinarian or veterinary technician should demonstrate or instruct the pet owner regarding the appropriate technique for applying Selarid topically to dogs and cats prior to first use.



Remove the applicator from the outer pouch using scissors or fold along diagonal line to expose nick; tear back at nick. Hold the applicator upright. Tap the narrow part of the applicator to ensure the contents remain within the main body of the applicator. Twist or snap back the tip. To administer the product, part the hair on the back of the animal at the base of the neck in front of the shoulder blades until the skin is visible. Place the tip of the applicator on the skin and squeeze the applicator 3 or 4 times to empty its entire contents directly onto the skin in one spot. Keeping the applicator squeezed, drag it away from the liquid and lift to remove. Check the applicator to ensure that it is empty. Do not massage the product into the skin. Due to alcohol content, do not apply to broken skin. Avoid contact between the product and fingers. Do not apply when the haircoat is wet. Bathing or shampooing the dog 2 or more hours after treatment will not reduce the effectiveness of Selarid against fleas or heartworm. Bathing or shampooing the cat 2 hours after treatment will not reduce the effectiveness of Selarid against fleas. Bathing or shampooing the cat 24 hours after treatment will not reduce the effectiveness of Selarid against heartworm. Stiff hair, clumping of hair, hair discoloration, or a slight powdery residue may be observed at the treatment site in some animals. These effects are temporary and do not affect the safety or effectiveness of the product. Discard empty applicators in your ordinary household refuse.

Flea Control in Dogs and Cats
For the prevention and control of flea infestations, Selarid should be administered at monthly intervals throughout the flea season, starting one month before fleas become active. In controlled laboratory studies >98% of fleas were killed within 36 hours. Results of clinical field studies using selamectin solution monthly demonstrated >90% control of flea infestations within 30 days of the first dose. Dogs and cats treated with selamectin solution, including those with pre-existing flea allergy dermatitis, showed improvement in clinical signs associated with fleas as a direct result of eliminating the fleas from the animals and their environment.

If the dog or cat is already infested with fleas when the first dose of Selarid is administered, adult fleas on the animal are killed and no viable fleas hatch from eggs after the first administration. However, an environmental infestation of fleas may persist for a short time after beginning treatment with Selarid because of the emergence of adult fleas from pupae.

Heartworm Prevention in Dogs and Cats
For the prevention of heartworm disease, Selarid must be administered on a monthly basis. Selarid may be administered year-round or at least within one month after the animal's first exposure to mosquitoes and monthly thereafter until the end of the mosquito season. The final dose must be given within one month after the last exposure to mosquitoes. If a dose is missed and a monthly interval between dosing is exceeded then immediate administration of Selarid and resumption of monthly dosing will minimize the opportunity for the development of adult heartworms. When replacing another heartworm preventive product in a heartworm disease prevention program, the first dose of Selarid must be given within a month of the last dose of the former medication.

Selamectin, the active ingredient in Selarid, is a macrocyclic lactone compound. These compounds effectively prevent the development of adult heartworms when administered to dogs and cats within one month of exposure to infective (L_3) *Dirofilaria immitis* larvae. Efficacy of macrocyclic lactones decreases below 100% in dogs, however, if first administered >2 months after exposure to infective larvae. Thus, in heartworm endemic regions, delaying initiation of heartworm prevention using Selarid beyond 2 months of first exposure to infective larvae (e.g., starting puppies and kittens at >8 weeks of age), or gaps of >2 months in the administration of Selarid during periods of heartworm transmission, increases the risk of the animal acquiring heartworms. Animals with unknown heartworm history that test negative for heartworms prior to the initiation of Selarid may be harboring pre-patent infections at the time Selarid was started. Testing such animals 3–4 months after initiation of Selarid would be necessary to confirm their negative heartworm status.

At the discretion of the veterinarian, cats ≥6 months of age may be tested to determine the presence of existing heartworm infections before beginning treatment with Selarid. Cats already infected with adult heartworms can be given Selarid monthly to prevent further infections.

Ear Mite Treatment in Dogs and Cats
For the treatment of ear mite (*O. cynotis*) infestations in dogs and cats, Selarid should be administered once as a single topical dose. A second monthly dose may be required in some dogs. Monthly use of Selarid will control any subsequent ear mite infestations. In the clinical field trials ears were not cleaned, and many animals still had debris in their ears after the second dose. Cleansing of the infested ears is recommended to remove the debris.

Sarcoptic Mange Treatment in Dogs
For the treatment of sarcoptic mange (*S. scabiei*) in dogs, Selarid should be administered once as a single topical dose. A second monthly dose may be required in some dogs. Monthly use of Selarid will control any subsequent sarcoptic mange mite infestations. Because of the difficulty in finding sarcoptic mange mites on skin scrapings, effectiveness assessments also were based on resolution of clinical signs. Resolution of the pruritus associated with the mite infestations was observed in approximately 50% of the dogs 30 days after the first treatment and in approximately 90% of the dogs 30 days after the second monthly treatment.

Tick Control in Dogs
For the control of tick (*Dermacentor variabilis*) infestations in dogs, Selarid should be administered on a monthly basis. In heavy tick infestations, complete efficacy may not be achieved after the first dose. In these cases, one additional dose may be administered two weeks after the previous dose, with monthly dosing continued thereafter.

Nematode Treatment in Cats
For the treatment and control of intestinal hookworm (*A. tubaeforme*) and roundworm (*T. cati*) infections, Selarid should be applied once as a single topical dose.

WARNINGS:

User Safety Warnings

Not for human use. Keep out of reach of children.

In humans, Selarid may be irritating to skin and eyes.

Reactions such as hives, itching and skin redness have been reported in humans. Individuals with known hypersensitivity to Selarid should use the product with caution or consult a health care professional. Selarid contains isopropyl alcohol and the preservative butylated hydroxytoluene (BHT).

Wash hands after use and wash off any product in contact with the skin immediately with soap and water.

If contact with eyes occurs, then flush eyes copiously with water; if wearing contact lenses, rinse the eyes first then remove contact lenses and continue to rinse for 5-10 minutes and seek medical attention. In case of ingestion by a human, contact a physician immediately.

The safety data sheet (SDS) provides more detailed occupational safety information. To obtain a SDS contact Norbrook at 1-866-591-5777 or www.norbrook.com.

Flammable - Keep away from heat, sparks, open flames or other sources of ignition.

Animal Safety Warnings

Do not use in sick, debilitated or underweight animals (see **TARGET ANIMAL SAFETY**).

PRECAUTIONS:
Prior to administration of Selarid, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infected dogs should be treated to remove adult heartworms. Selarid is not effective against adult *D. immitis* and, while the number of circulating microfilariae may decrease following treatment, Selarid is not effective for microfilariae clearance.
Hypersensitivity reactions have not been observed in dogs with patent heartworm infections administered selamectin solution (see **TARGET ANIMAL SAFETY**).

ADVERSE REACTIONS:
Pre-Approval Clinical Trials:
Following treatment with selamectin solution, transient localized alopecia with or without inflammation at or near the site of application was observed in approximately 1% of 691 treated cats. Other signs observed (≤0.5% of 1743 treated cats and dogs) included vomiting, loose stool or diarrhea with or without blood, anorexia, lethargy, salivation, tachypnea, and muscle tremors.

Post-Approval Experience (2021):
The following adverse events are based on post-approval adverse drug experience reporting for selamectin solution. Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using this data.
The following adverse events reported for **dogs** are listed in decreasing order of reporting frequency:
Lethargy, vomiting, diarrhea, anorexia, generalized pruritus, seizures, application site reactions (including alopecia, lesions, erythema, pruritus, and inflammation), tremors, ataxia, death, and dermatitis.
The following adverse events reported for **cats** are listed in decreasing order of reporting frequency:
Application site reactions (including alopecia, lesions, erythema, pruritus, inflammation, vesicles, blisters, and excoriations), lethargy, anorexia, vomiting, death, generalized pruritus, diarrhea, ataxia, fever, generalized alopecia, tremors, hypersalivation, dermatitis, and seizures.

CONTACT INFORMATION:
Contact Norbrook at 1-866-591-5777 or www.norbrook.com.
To report suspected adverse drug experiences, contact Norbrook at 1-866-591-5777. For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae

TARGET ANIMAL SAFETY:
Selamectin solution has been tested safe in over 100 different pure and mixed breeds of healthy dogs and over 15 different pure and mixed breeds of healthy cats, including pregnant and lactating females, breeding males and females, puppies six weeks of age and older, kittens eight weeks of age and older, and avermectin-sensitive collies. A kitten, estimated to be 5–6 weeks old (0.3 kg), died 8 ½ hours after receiving a single treatment of selamectin solution at the recommended dosage. The kitten displayed clinical signs which included muscle spasms, salivation and neurological signs. The kitten was a stray with an unknown history and was malnourished and underweight (see **WARNINGS**).

DOGS: In safety studies, selamectin solution was administered at 1, 3, 5, and 10 times the recommended dose to six-week-old puppies, and no adverse reactions were observed. The safety of selamectin solution administered orally also was tested in case of accidental oral ingestion. Oral administration of selamectin solution at the recommended topical dose in 5- to 8-month-old beagles did not cause any adverse reactions. In a pre-clinical study selamectin was dosed orally to ivermectin-sensitive collies. Oral administration of 2.5, 10, and 15 mg/kg in this dose escalating study did not cause any adverse reactions; however, eight hours after receiving 5 mg/kg orally, one avermectin-sensitive collie became ataxic for several hours, but did not show any other adverse reactions after receiving subsequent doses of 10 and 15 mg/kg orally. In a topical safety study conducted with avermectin-sensitive collies at 1, 3 and 5 times the recommended dose of selamectin solution, salivation was observed in all treatment groups, including the vehicle control. Selamectin solution also was administered at 3 times the recommended dose to heartworm infected dogs, and no adverse effects were observed.

CATS: In safety studies, selamectin solution was applied at 1, 3, 5, and 10 times the recommended dose to six-week-old kittens. No adverse reactions were observed. The safety of selamectin solution administered orally also was tested in case of accidental oral ingestion. Oral administration of the recommended topical dose of selamectin solution to cats caused salivation and intermittent vomiting. Selamectin solution also was applied at 4 times the recommended dose to patent heartworm infected cats, and no adverse reactions were observed.

In well-controlled clinical studies, selamectin solution was used safely in animals receiving other frequently used veterinary products such as vaccines, anthelmintics, antiparasitics, antibiotics, steroids, collars, shampoos and dips.

STORAGE CONDITIONS: Store below 86°F (30°C).

HOW SUPPLIED: Available in eight separate dose strengths for dogs and cats of different weights (see **DOSAGE**). Selarid for puppies and kittens is available in cartons containing 3 single dose applicators. Selarid for cats and dogs is available in cartons containing 6 single dose applicators.

Approved by FDA under ANADA # 200-663

Made in Ireland

Manufactured by:
Norbrook Manufacturing Ltd.
Rossmore Industrial Estate
Monaghan, Co. Monaghan
Ireland.

Revised Jul 2024

Norbrook®

Client Information About

Selarid®

(selamectin)

Selarid (pronounced "Sel-a-rid")

Generic name: selamectin ("sel-a-mec-tin")

This summary contains important information about Selarid®. You should read this information before you start using Selarid on your dog or cat 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 if you want to know more about Selarid.

What is Selarid?
Selarid is a topical parasiticide that is applied to the skin of dogs six weeks of age and older and cats eight weeks of age and older to kill adult fleas and prevent flea eggs from hatching, prevent heartworm disease and protect your pet against other parasites (see below).

Why has my veterinarian prescribed Selarid?
Selarid has been prescribed by your veterinarian to treat, prevent and/or control the following parasites in your dog or cat:

Dog Parasites:
- Control and prevention of flea infestation (*Ctenocephalides felis*)
- Prevention of heartworm disease (*Dirofilaria immitis*)
- Treatment and control of ear mite infestation (*Otodectes cynotis*)
- Treatment and control of sarcoptic mange (*Sarcoptes scabiei*)
- Control of the American Dog Tick (*Dermacentor variabilis*)

Cat Parasites:
- Control and prevention of flea infestation (*Ctenocephalides felis*)
- Prevention of heartworm disease (*Dirofilaria immitis*)
- Treatment and control of ear mite infestation (*Otodectes cynotis*)
- Treatment and control of intestinal worms Roundworm (*Toxocara cati*)
  Hookworm (*Ancylostoma tubaeforme*)

What should I discuss with my veterinarian before Selarid is prescribed?
Your veterinarian is best suited to discuss and recommend appropriate medications for your dog or cat. It is important to discuss your pet's health history with your veterinarian so he/she can decide if Selarid is right for your animal.

Selarid should not be used in sick, debilitated or underweight animals.

Dogs should be tested for heartworm disease prior to giving Selarid. If your dog tests positive for adult heartworms, your veterinarian can recommend appropriate treatment.
Dogs infected with adult heartworms can safely be given Selarid.
If your cat is older than six months of age, your veterinarian may decide to test him/her for heartworm disease before prescribing Selarid. Cats infected with adult heartworms can be given Selarid to prevent further infections.

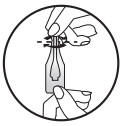
What dose of Selarid do I use on my dog or cat?
Your veterinarian will recommend the appropriate dose for your dog or cat based on your animal's body weight.
You should not administer Selarid to dogs younger than 6 weeks of age or cats younger than 8 weeks of age. Selarid is available in eight separate dose strengths for dogs and cats of different weights.

What should I do if I do not give Selarid on time or miss a dose?
If you forget to apply a monthly dose of Selarid, immediately apply Selarid, resume monthly applications, and notify your veterinarian.

What if I administer more than the prescribed amount of Selarid to my dog or cat?
Contact your veterinarian if you administer more than the prescribed amount of Selarid.

How should Selarid be applied?

- Remove the applicator from the outer pouch using scissors or fold along diagonal line to expose nick; tear back at nick.



- Hold the applicator upright. Tap the narrow part of the applicator to ensure the contents remain within the main body of the applicator. Twist or snap back the tip.

- Part the hair on the back of the animal at the base of the neck, in front of the shoulder blades, until the skin is visible.

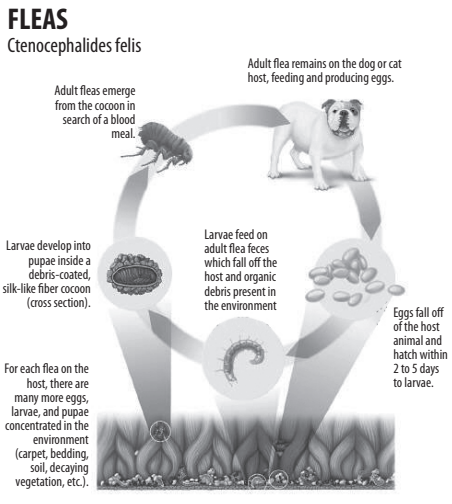
- Apply the tip of the Selarid applicator directly to the skin. Squeeze the applicator firmly 3–4 times in one spot until empty. Keep applicator compressed on the final squeeze to avoid drawing liquid back into applicator. Avoid contact between Selarid and your fingers.
- While keeping applicator squeezed, drag it away from liquid and lift up to remove.
- Ensure applicator is empty.

Do not massage Selarid into the skin.
Do not apply when the haircoat is wet.
Do not apply to broken skin – Selarid contains alcohol.

Stiff hair, clumping of hair, hair discoloration, or a slight powdery residue may be observed at the site in some animals. These effects are usually temporary and do not affect the safety or effectiveness of the product.

Can I give my pet a bath after applying Selarid?
Yes. Bathing or shampooing the dog 2 or more hours after treatment will not reduce the effectiveness of Selarid against fleas or heartworm. Bathing or shampooing the cat 24 hours after treatment will not reduce the effectiveness of Selarid against fleas or heartworm.

When can I play with my pet following treatment with Selarid?
You should avoid contact with application site when wet. You may hold or play with your pet any time after the area on which Selarid was applied is dry.



I see fleas on my dog or cat. Is Selarid working?
Selarid kills adult fleas and prevents flea eggs from hatching. You may occasionally see a few fleas on dogs or cats treated with Selarid but more than 98% of adult fleas are killed within 36 hours.
Immature stages of the flea called pupae may be present in your pets' environment (yard, flooring, carpet, bedding, etc.). These pupae are not killed by parasiticides (including Selarid) and as such may emerge as adult fleas.
These adult fleas may hop onto your pet at anytime. They must be exposed to Selarid on your dog or cat before being killed. It can take from 3–5 weeks (or longer depending on environmental conditions) for most fleas to complete their 4-stage life cycle (egg, larvae, pupae, and adult) and reach the adult stage before being seen on your pet. Due to the presence of immature flea stages in infested environments it can take up to 2 to 3 monthly applications for Selarid to maximally control the infestation of fleas in the environment. Once the flea population is controlled you will be less likely to see fleas.

I see ticks on my dog. Is Selarid working?
Selarid controls tick infestations only due to the American Dog Tick (*Dermacentor variabilis*), a tick commonly found on dogs. There are other common species of ticks that are not killed or controlled by Selarid. Your veterinarian can recommend appropriate products to control or kill ticks common to your area. For the control of the American Dog Tick, Selarid should be applied once a month; however, your veterinarian may recommend a second administration applied 14 days after the first dose if your dog has a heavy tick infestation and/or recommend additional tick control methods. It may take up to 5 days to kill the majority of ticks on your dog.

What are the possible side effects of Selarid?
Following the use of Selarid, the following side effects have been seen, listed in decreasing order of frequency for each species.

Dogs- Sluggishness, vomiting, diarrhea (with or without blood), decreased appetite, generalized itching, seizures, hair loss or skin redness at the application site, trembling, incoordination, skin inflammation, drooling, and rapid breathing.

In some cases, death has been reported in dogs.

Cats- Hair loss at the site of application with or without redness, flaking, or itching, sluggishness, decreased appetite, vomiting, generalized itching, diarrhea (with or without blood), incoordination, fever, hair loss, trembling, drooling, skin inflammation, and seizures.

Severe application site reactions like blisters, scabbing, and infection have been reported in cats.

In some cases, death has been reported in cats.

Can Selarid be given with other medicines?
In well-controlled clinical studies, selamectin solution was used safely in dogs and cats receiving other veterinary products such as vaccines, anthelmintics, antiparasitics, antibiotics, steroids, collars, shampoos and dips.
Tell your veterinarian about all medicines you have given your dog or cat in the past, and any medicines that you are planning to use with Selarid. This should include other medicines that you can get without a prescription. Your veterinarian may want to check that all of your dog's or cat's medicines can be given together.

How should Selarid be stored?
Selarid is flammable – Keep away from heat, sparks, open flames or other sources of ignition. Store below 86°F (30°C). After application, empty applicators can be placed in your normal household refuse for disposal.

What else should I know about Selarid?

Selarid is not for use in humans.

Selarid should be kept out of reach of children.

In humans, Selarid may be irritating to skin and eyes. Reactions such as hives, itching and skin redness have been reported in humans. Individuals with known hypersensitivity to Selarid should use the product with caution or consult a health care professional. Selarid contains isopropyl alcohol and the preservative butylated hydroxytoluene (BHT).

Wash hands after use and wash off any product in contact with skin immediately with soap and water. In case of human ingestion contact a doctor immediately.

Revised: Jul 2024

Manufactured by:
Norbrook Manufacturing Ltd.
Rossmore Industrial Estate
Monaghan, Co. Monaghan
Ireland

966670I03

Norbrook®

Midamox® *for Dogs*

(imidacloprid + moxidectin)

Topical Solution

Once-a-month topical solution for the prevention of heartworm disease, the treatment of circulating microfilariae, kills adult fleas, is indicated for the treatment of flea infestations, the treatment and control of sarcoptic mange, as well as the treatment and control of intestinal parasite infections in dogs and puppies that are at least 7 weeks of age and that weigh at least 3 lbs.

WARNING

- **DO NOT ADMINISTER THIS PRODUCT ORALLY**
- **For the first 30 minutes after application ensure that dogs cannot lick the product from application sites on themselves or other treated animals.**
- **Children should not come in contact with application sites for two (2) hours after application.**

(See Contraindications, Warnings, Human Warnings, and Adverse Reactions, for more information)

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

DESCRIPTION:
Midamox for Dogs (10 % imidacloprid + 2.5 % moxidectin) is a colorless to yellow ready-to-use solution packaged in single dose applicators for topical treatment of dogs. The formulation and dosage schedule are designed to provide a minimum of 4.5 mg/lb (10 mg/kg) imidacloprid and 1.1 mg/lb (2.5 mg/kg) moxidectin based on body weight.

Imidacloprid is a chloronicotinyl nitroguanidine insecticide. The chemical name for imidacloprid is 1-[(6-Chloro-3-pyridinyl)methyl]-N-nitro-2-imidazolidinimine. Moxidectin is a semisynthetic macrocydic lactone endectocide derived from the actinomycete *Streptomycetes cyaneogriseus noncyanogenus*. The chemical name for moxidectin is [6R, 23E, 25S(E)]-5-O- Demethyl-28-de-oxy-25-(1,3-dimethyl-1-butenyl)-6,28-epoxy-23-(methoxyimino) milbemycin B.

INDICATIONS:
Midamox for Dogs is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and the treatment of *Dirofilaria immitis* circulating microfilariae in heartworm-positive dogs. *Midamox for Dogs* kills adult fleas and is indicated for the treatment of flea infestations (*Ctenocephalides felis*). *Midamox for Dogs* is indicated for the treatment and control of sarcoptic mange caused by *Sarcoptes scabiei* var. *canis*. *Midamox for Dogs* is also indicated for the treatment and control of the following intestinal parasites:

Intestinal Parasite		Intestinal Stage		
		Adult	Immature Adult	Fourth Stage Larvae
Hookworm Species	*Ancylostoma caninum*	X	X	X
	Uncinaria stenocephala	X	X	X
Roundworm Species	*Toxocara canis*	X		X
	Toxascaris leonina	X		
Whipworm	*Trichuris vulpis*	X		

DOSAGE AND ADMINISTRATION:
The recommended minimum dose is 4.5 mg/lb (10 mg/kg) imidacloprid and 1.1 mg/lb (2.5 mg/kg) moxidectin, once a month, by topical administration.
Do not apply to irritated skin.

1. Remove the applicator from the outer pouch using scissors or fold along diagonal line to expose nick; tear back at nick. As specified in the following table, administer the entire contents of the *Midamox for Dogs* (imidacloprid and moxidectin) applicator that correctly corresponds with the body weight of the dog.

Dog (lbs.)	*Midamox for Dogs*	Volume (mL)	Imidacloprid (mg)	Moxidectin (mg)
3–9	*Midamox 9*	0.4	40	10
9.1–20	*Midamox 20*	1.0	100	25
20.1–55	*Midamox 55*	2.5	250	62.5
55.1–88	*Midamox 88*	4.0	400	100
88.1–110*	*Midamox 110*	5.0	500	125

* Dogs over 110 lbs. should be treated with the appropriate combination of *Midamox for Dogs* applicators.

2. Hold the applicator upright.
3. Tap the narrow part of the applicator to ensure the contents remain within the main body of the applicator.
4. Twist or snap back the tip.

5. The dog should be standing for application. Part the hair on the back of the dog between the shoulder blades until the skin is visible. For dogs weighing 20 lbs. or less, place the tip of the applicator on the skin and apply the entire contents directly on the exposed skin at one spot between the shoulder blades.
For dogs weighing more than 20 lbs., place the tip of the applicator on the skin and apply the entire contents directly on the exposed skin at 3 or 4 spots on the top of the backline from the base of the neck to the upper back in an area inaccessible to licking. Do not apply an amount of solution at any one location that could run off the side of the dog.

Do not let this product get in your dog's mouth or eyes. **Do not allow the dog to lick any of the application sites for 30 minutes.** In households with multiple pets, keep each treated dog separated from other treated dogs and other pets for 30 minutes after application to prevent licking the application sites.
(See WARNINGS.) Contact with eyes can lead to eye irritation and corneal ulceration. If contact with eyes occurs, hold the dog's eyelids open, flush thoroughly with water, and contact your veterinarian.

Stiff hair, a damp appearance of the hair, pink skin, or a slight powdery residue may be observed at the application site on some animals. This is temporary and does not affect the safety and effectiveness of the product.

Shampooing 90 minutes after treatment does not reduce the effectiveness of *Midamox for Dogs* in the prevention of heartworm disease. Shampooing or water immersion 4 days after treatment will not reduce the effectiveness of *Midamox for Dogs* in the treatment of flea infestations. However, shampooing as often as once weekly may reduce the effectiveness of the product against fleas.

Heartworm Prevention: For prevention of heartworm disease, *Midamox for Dogs* should be administered at one-month intervals. *Midamox for Dogs* may be administered year-round or at a minimum should start one month before the first expected exposure to mosquitoes and should continue at monthly intervals until one month after the last exposure to mosquitoes. If a dose is missed and a 30-day interval between doses is exceeded, administer *Midamox for Dogs* immediately and resume the monthly dosing schedule. When replacing another heartworm preventative product in a heartworm prevention program, the first treatment with *Midamox for Dogs* should be given within one month of the last dose of the former medication.

Treatment of Circulating Microfilaria: For the treatment of circulating *D. immitis* microfilaria in heartworm-positive dogs, *Midamox for Dogs* should be administered at one-month intervals. Treatment with an approved adulticide therapy is recommended because *Midamox for Dogs* is not effective for the treatment of adult *D. immitis*.
(See PRECAUTIONS.)

Flea Treatment: For the treatment of flea infestations, *Midamox for Dogs* should be administered at one-month intervals. If the dog is already infested with fleas when the first dose of *Midamox for Dogs* is administered, adult fleas on the dog will be killed. However, reinfestation from the emergence of preexisting pupae in the environment may continue to occur for six weeks or longer after treatment is initiated. Dogs treated with imidacloprid, including those with pre-existing flea allergy dermatitis have shown clinical improvement as a direct result of elimination of fleas from the dog.

Treatment and Control of Intestinal Nematode Infections: For the treatment and control of intestinal hookworm infections caused by *Ancylostoma caninum* and *Uncinaria stenocephala* (adults, immature adults and fourth stage larvae) and roundworm infections caused by *Toxocara canis* (adults and fourth stage larvae), and *Toxascaris leonina* (adults), and whipworm infections caused by *Trichuris vulpis* (adults), *Midamox for Dogs* should be administered once as a single topical dose.

Treatment and Control of Sarcoptic Mange: For the treatment and control of sarcoptic mange caused by *Sarcoptes scabiei* var. *canis*, *Midamox for Dogs* should be administered as a single topical dose. A second monthly dose may be administered if necessary.

CONTRAINDICATIONS:
Do not administer this product orally. (See WARNINGS.)
Do not use this product (containing 2.5% moxidectin) on cats.

WARNINGS
For the first 30 minutes after application:
Ensure that dogs cannot lick the product from application sites on themselves or other treated dogs, and
Separate treated dogs from one another and from other pets to reduce the risk of accidental ingestion.
Ingestion of this product by dogs may cause serious adverse reactions including depression, salivation, dilated pupils, incoordination, panting, and generalized muscle tremors.
In avermectin sensitive dogs,[a] the signs may be more severe and may include coma and death.[b]
[a] Some dogs are more sensitive to avermectins due to a mutation in the MDR1 gene. Dogs with this mutation may develop signs of severe avermectin toxicity if they ingest this product. The most common breeds associated with this mutation include Collies and Collie crosses.
[b] Although there is no specific antagonist for avermectin toxicity, even severely affected dogs have completely recovered from avermectin toxicity with intensive veterinary supportive care.

HUMAN WARNINGS:
Not for human use. Keep out of the reach of children.
Children should not come in contact with application sites for two (2) hours after application.
Causes eye irritation. Harmful if swallowed. Do not get in eyes or on clothing. Avoid contact with skin. Exposure to the product has been reported to cause headache; dizziness; and redness, burning, tingling, or numbness of the skin.
Wash hands thoroughly with soap and warm water after handling.
If contact with eyes occurs, hold eyelids open and flush with copious amounts of water for 15 minutes. If eye irritation develops or persists, contact a physician. If swallowed, call poison control center or physician immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or physician. People with known hypersensitivity to benzyl alcohol, imidacloprid or moxidectin should administer the product with caution. In case of allergic reaction, contact a physician. If contact with skin or clothing occurs, take off contaminated clothing. Wash skin immediately with plenty of soap and water. Call a poison control center or physician for treatment advice.

The Safety Data Sheet (SDS) provides additional occupational safety information. For product questions, to report adverse reactions, or for a copy of the Safety Data Sheet (SDS), call Norbrook at 1-866-591-5777.

PRECAUTIONS:
Do not dispense dose applicators without complete safety and administration information.

Use with caution in sick, debilitated, or underweight animals. The safety of *Midamax for Dogs* has not been established in breeding, pregnant, or lactating dogs. The safe use of *Midamax for Dogs* has not been established in puppies and dogs less than 7 weeks of age or less than 3 lbs. body weight.

Prior to administration of *Midamax for Dogs*, dogs should be tested for existing heartworm infection. At the discretion of the veterinarian, infected dogs should be treated with an adulticide to remove adult heartworms. The safety of *Midamax for Dogs* has not been evaluated when administered on the same day as an adulticide. *Midamax for Dogs* is not effective against adult *D. immitis*. Although the number of circulating microfilariae is substantially reduced in most dogs following treatment with *Midamax for Dogs*, the microfilaria count in some heartworm-positive dogs may increase or remain unchanged following treatment with *Midamax for Dogs* alone or in a dosing regimen with melarsomine dihydrochloride.
(See ADVERSE REACTIONS and ANIMAL SAFETY – Safety Study in Heartworm-Positive Dogs.)

Imidacloprid and moxidectin has not been evaluated in heartworm-positive dogs with Class 4 heartworm disease.

ADVERSE REACTIONS:
Heartworm-Negative Dogs
Field Studies: Following treatment with imidacloprid and moxidectin or an active control, dog owners reported the following post-treatment reactions:

OBSERVATION	imidacloprid + moxidectin n=128	Active Control n=68
Pruritus	19 dogs (14.8%)	7 dogs (10.3%)
Residue	9 dogs (7.0%)	5 dogs (7.4%)
Medicinal Odor	5 dogs (3.9%)	None observed
Lethargy	1 dog (0.8%)	1 dog (1.5%)
Inappetence	1 dog (0.8%)	1 dog (1.5%)
Hyperactivity	1 dog (0.8%)	None observed

During a field study using 61 dogs with pre-existing flea allergy dermatitis, one (1.6 %) dog experienced localized pruritus immediately after imidacloprid application, and one investigator noted hyperkeratosis at the application site of one dog (1.6 %).

In a field safety and effectiveness study, imidacloprid and moxidectin was administered to 92 client-owned dogs with sarcoptic mange. The dogs ranged in age from 2 months to 12.5 years and ranged in weight from 3 to 231.5 pounds. Adverse reactions in dogs treated with imidacloprid and moxidectin included hematochezia, diarrhea, vomiting, lethargy, inappetence, and pyoderma.

Laboratory Effectiveness Studies: One dog in a laboratory effectiveness study experienced weakness, depression, and unsteadiness between 6 and 9 days after application with imidacloprid and moxidectin. The signs resolved without intervention by day 10 post-application. The signs in this dog may have been related to peak serum levels of moxidectin, which vary between dogs, and occur between 1 and 21 days after application of imidacloprid and moxidectin.

The following clinical observations also occurred in laboratory effectiveness studies following application with imidacloprid and moxidectin and may be directly attributed to the drug or may be secondary to the intestinal parasite burden or other underlying conditions in the dogs: diarrhea, bloody stools, vomiting, anorexia, lethargy, coughing, ocular discharge and nasal discharge. Observations at the application sites included damp, stiff or greasy hair, the appearance of a white deposit on the hair, and mild erythema, which resolved without treatment within 2 to 48 hours.

Heartworm-Positive Dogs
Field Study: A 56-day field safety study was conducted in 214 *D. immitis* heartworm and microfilaria positive dogs with Class 1, 2 or 3 heartworm disease. All dogs received imidacloprid and moxidectin on Study Days 0 and 28; 108 dogs also received melarsomine dihydrochloride on Study Days – 14, 14, and 15. All dogs were hospitalized for a minimum of 12 hours following each treatment. Effectiveness against circulating *D. immitis* microfilariae was > 90 % at five of six sites; however, one site had an effectiveness of 73.3 %. The microfilaria count in some heartworm-positive dogs increased or remained unchanged following treatment with imidacloprid and moxidectin alone or in a dosing regimen with melarsomine dihydrochloride.

Following treatment with imidacloprid and moxidectin alone or in a dosing regimen with melarsomine dihydrochloride, the following adverse reactions were observed:

Adverse Reaction	Dogs Treated with imidacloprid + moxidectin for Dogs Only n=106	Dogs Treated with imidacloprid + moxidectin for Dogs + Melarsomine n=108
Cough	24 (22.6%)	25 (23.1%)
Lethargy	14 (13.2%)	42 (38.9%)
Vomiting	11 (10.4%)	18 (16.7%)
Diarrhea, including hemorrhagic	10 (9.4%)	22 (20.4%)
Inappetence	7 (6.6%)	19 (17.6%)
Dyspnea	6 (5.7%)	10 (9.3%)
Tachypnea	1 (<1%)	7 (6.5%)
Pulmonary Hemorrhage	0	1 (<1%)
Death	0	3 (2.8%)

Three dogs treated with imidacloprid and moxidectin in a dosing regimen with melarsomine dihydrochloride died of pulmonary embolism from dead and dying heartworms. One dog, treated with imidacloprid and moxidectin and melarsomine dihydrochloride, experienced pulmonary hemorrhage and responded to supportive medical treatment. Following the first treatment with imidacloprid and moxidectin alone, two dogs experienced adverse reactions (coughing, vomiting, and dyspnea) that required hospitalization. In both groups, there were more adverse reactions to imidacloprid and moxidectin following the first treatment than the second treatment.

To report a suspected adverse reaction, call 1-866-591-5777.

Post-Approval Experience 2022
The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse events are reported to FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using this data.
The following adverse events reported in dogs are listed in decreasing order of reporting frequency: depression/lethargy, pruritus, vomiting, diarrhea, anorexia, application site reactions (alopecia, pruritus, erythema, and lesions, including blisters), hyperactivity, ataxia, trembling, seizures, panting, hypersalivation, anaphylaxis/anaphylactic reactions (hives, facial swelling, edema of the head), and corneal ulceration.

Serious reactions, including neurologic signs and death have been reported when cats have been exposed (orally and topically) to this product.
In humans, nausea, numbness or tingling of the mouth/lips and throat, ocular and dermal irritation, pruritus, headache, vomiting, diarrhea, depression and dyspnea have been reported following exposure to this product.

Contact Information:
For product questions, to report suspected adverse drug experiences, or for a copy of the Safety Data Sheet (SDS), call Norbrook at 1-866-591-5777.

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

ANIMAL SAFETY:
Heartworm-Negative Dogs
Field Study: In a controlled, double-masked, field safety study, imidacloprid and moxidectin was administered to 128 dogs of various breeds, 3 months to 15 years of age, weighing 4 to 157 pounds. Imidacloprid and moxidectin was used safely in dogs concomitantly receiving ACE inhibitors, anticonvulsants, antihistamines, antimicrobials, chondroprotectants, corticosteroids, immunotherapeutics, MAO inhibitors, NSAIDs, ophthalmic medications, sympathomimetics, synthetic estrogens, thyroid hormones, and urinary acidifiers. Owners reported the following signs in their dogs after application of imidacloprid and moxidectin: pruritus, flaky/greasy residue at the treatment site, medicinal odor, lethargy, inappetence, and hyperactivity.
(See ADVERSE REACTIONS.)

Safety Study in Puppies: Imidacloprid and moxidectin was applied topically at 1, 3 and 5X the recommended dose to 7-week-old Beagle puppies once every 2 weeks for 6 treatments on days 0, 14, 28, 42, 56, and 70. Loose stools and diarrhea were observed in all groups, including the controls, throughout the study. Vomiting was seen in one puppy from the 1X treatment group (day 57), in two puppies from the 3X treatment group (days 1 and 79), and in one puppy from the 5X treatment group (day 1). Two puppies each in the 1X, 3X, and 5X groups had decreased appetites within 24 hours post-dosing. One puppy in the 1X treatment group had pruritus for one hour following the fifth treatment. A puppy from the 5X treatment group displayed rapid, difficult breathing from 4 to 8 hours following the second treatment.

Dermal Dose Tolerance Study: Imidacloprid and moxidectin was administered topically to 8-month-old Beagle dogs at 10X the recommended dose once. One dog showed signs of treatment site irritation after application. Two dogs vomited, one at 6 hours and one at 6 days post-treatment. Increased RBC, hemoglobin, activated partial thromboplastin, and direct bilirubin were observed in the treated group. Dogs in the treated group did not gain as much weight as the control group.

Oral Safety Study in Beagles: Imidacloprid and moxidectin was administered once orally at the recommended topical dose to 12 dogs. Six dogs vomited within 1 hour of receiving the test article, 2 of these dogs vomited again at 2 hours, and 1 dog vomited again up to 18 hours post-dosing. One dog exhibited shaking (nervousness) 1 hour post-dosing. Another dog exhibited abnormal neurological signs (circling, ataxia, generalized muscle tremors, and dilated pupils with a slow pupillary light response) starting at 4 hours post-dosing through 18 hours post-dosing. Without treatment, this dog was neurologically normal at 24 hours and had a normal appetite by 48 hours post-dosing.
(See CONTRAINDICATIONS.)

Dermal Safety Study in Ivermectin-Sensitive Collies: Imidacloprid and moxidectin was administered topically at 3 and 5X the recommended dose every 28 days for 3 treatments to Collies which had been prescreened for avermectin sensitivity. No clinical abnormalities were observed.

Oral Safety Study in Ivermectin-Sensitive Collies: Imidacloprid and moxidectin was administered orally to 5 pre-screened ivermectin-sensitive Collies. The Collies were asymptomatic after ingesting 10 % of the minimum labeled dose. At 40 % of the minimum recommended topical dose, 4 of the dogs experienced neurological signs indicative of avermectin toxicity including depression, ataxia, mydriasis, salivation, muscle fasciculation, and coma, and were euthanized.
(See CONTRAINDICATIONS.)

Heartworm-Positive Dogs
Laboratory Safety Study in Heartworm-Positive Dogs: Imidacloprid and moxidectin was administered topically at 1 and 5X the recommended dose every 14 days for 3 treatments to dogs with adult heartworm infections and circulating microfilaria. At 5X, one dog was observed vomiting three hours after the second treatment. Hypersensitivity reactions were not seen in the 5X treatment group. Microfilaria counts decreased with treatment.

STORAGE INFORMATION:
Store below 77°F (25°C). Excursions are permitted up to 104°F (40°C) however such exposure should be minimized. Do not remove the applicator from the pouch until ready to use. Do not use after the expiry date which is stated on the carton.

HOW SUPPLIED:
Applications Per Package,
6 x 0.4 mL applicators, 6 x 1.0 mL applicators, 6 x 2.5 mL applicators, 6 x 4.0 mL applicators, 6 x 5.0 mL applicators
Approved by FDA under ANADA # 200-716

Made in Ireland

Manufactured by:
Norbrook Manufacturing Ltd.
Rossmore Industrial Estate
Monaghan, Co. Monaghan
Ireland

Midamax® is a trademark of
Norbrook Laboratories Limited

Revised July 2023

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Norbrook®

Midamox® *for Cats*

(imidacloprid + moxidectin)

Topical Solution

Once-a-month topical solution for cats for the prevention of heartworm disease, kills adult fleas, is indicated for the treatment of flea infestations, as well as the treatment and control of ear mite infestations and intestinal parasite infections in cats and kittens 9 weeks of age and older and that weigh at least 2 lbs.

Once-a-month topical solution for ferrets for the prevention of heartworm disease, kills adult fleas, and is indicated for the treatment of flea infestations. Indicated for ferrets that weigh at least 2 lbs.

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

DESCRIPTION:
Midamox for Cats (10 % imidacloprid + 1 % moxidectin) is a colorless to yellow ready-to-use solution packaged in single-dose applicators for topical treatment of cats. The formulation and dosage schedule are designed to provide a minimum of 4.5 mg/lb (10.0 mg/kg) imidacloprid and 0.45 mg/lb (1.0 mg/kg) moxidectin based on body weight.

Imidacloprid is a chloronicotinyl nitroguanidine insecticide. The chemical name of imidacloprid is 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine. Moxidectin is a semisynthetic macrocyclic lactone endectocide derived from the actinomycete *Streptomycetes cyaneogriseus noncyanogenus*. The chemical name of moxidectin is [6R, 23E, 25S(E)]-5-O-Demethyl -28-deoxy-25-(1,3-dimethyl-1-butenyl)-6,28-epoxy-23-(methoxyimino) milbemycin B.

INDICATIONS:
Midamox for Cats is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*. *Midamox for Cats* kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment of flea infestations. *Midamox for Cats* is also indicated for the treatment and control of ear mite (*Otodectes cynotis*) infestations and the following intestinal parasites:

Intestinal Parasite		Intestinal Stage		
		Adult	Immature Adult	Fourth Stage Larvae
Hookworm Species	*Ancylostoma tubaeforme*	X	X	X
Roundworm Species	*Toxocara cati*	X		X

WARNINGS:
Do not use on sick, debilitated, or underweight cats (see ADVERSE REACTIONS). Do not use on cats less than 9 weeks of age or less than 2 lbs. body weight.

HUMAN WARNINGS:
Not for human use. Keep out of the reach of children. Children should not come in contact with the application site for 30 minutes after application.

Causes eye irritation. Harmful if swallowed. Do not get in eyes or on clothing. Avoid contact with skin. Exposure to the product has been reported to cause headache; dizziness; and redness, burning, tingling, or numbness of the skin.

Wash hands thoroughly with soap and warm water after handling.

If contact with eyes occurs, hold eyelids open and flush with copious amounts of water for 15 minutes. If eye irritation develops or persists, contact a physician. If swallowed, call poison control center or physician immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or physician. People with known hypersensitivity to benzyl alcohol, imidacloprid or moxidectin should administer the product with caution. In case of allergic reaction, contact a physician. If contact with skin or clothing occurs, take off contaminated clothing. Wash skin immediately with plenty of soap and water. Call a poison control center or physician for treatment advice.

The Safety Data Sheet (SDS) provides additional occupational safety information. For a copy of the Safety Data Sheet (SDS) or to report adverse reactions call 1-866-591-5777.

PRECAUTIONS:
Do not dispense dose applicators without complete safety and administration information.

Avoid oral ingestion. Cats may experience hypersalivation, tremors, vomiting and decreased appetite if *Midamox for Cats* is inadvertently administered orally or through grooming/licking of the application site.

The safety of *Midamox for Cats* has not been established in breeding, pregnant, or lactating cats.

The effectiveness of *Midamox for Cats* against heartworm infections (*D. immitis*) after bathing has not been evaluated in cats.

Use of this product in geriatric patients with subclinical conditions has not been adequately studied. Several otherwise healthy, thin geriatric cats experienced prolonged lethargy and sleepiness after using this drug. **(See ADVERSE REACTIONS.)**

ADVERSE REACTIONS:
Field Study: Following treatment with imidacloprid and moxidectin or an active control, cat owners reported the following post-treatment reactions:

OBSERVATION	Imidacloprid + moxidectin n = 113	Active Control n = 38
Lethargy (protracted sleeping, poorly responsive)	3 cats* (2.7%)	None observed
Behavioral changes (e.g., agitated, excessive grooming, hiding, pacing, spinning)	9 cats (8.0%)	1 cat (2.6%)
Discomfort (e.g., scratching, rubbing, head-shaking)	5 cats (4.4%)	None observed
Hypersalivation (within 1 hour after treatment)	3 cats (2.7%)	None observed
Polydipsia	3 cats (2.7%)	None observed
Coughing and gagging	1 cat (0.9%)	None observed

* These three cats were from the same household and included one 13-yr-old cat in good health, one 15-yr-old FIV positive cat in good health, and one 15-yr-old, underweight cat in fair health. Lethargy was noted for 24 to 36 hrs after the first treatment only; one cat was unsteady at 48 hrs. These cats were not on other medications.

During another field study, a 16-year-old cat with renal disease slept in the same place without moving for two days following application. **(See PRECAUTIONS.)**

Laboratory Effectiveness Studies: Imidacloprid and moxidectin was administered at the recommended dose to 215 cats in 20 effectiveness studies. One random-sourced cat exhibited signs consistent with either moxidectin toxicity or viral respiratory disease and died 26 hours after product application; necropsy findings were inconclusive as to the cause of death. A second cat that became ill 3 days after application of imidacloprid and moxidectin responded to treatment for respiratory infection and completed the study. A third cat became ill on day 3 and died with signs and lesions attributable to panleukopenia on day 7 after moxidectin application.

Post-Approval Experience: The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse reactions are reported to FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using this data. The following adverse events in cats are listed in decreasing order of reporting frequency: hypersalivation, depression/lethargy, application site reactions (alopecia, pruritus, lesions, and erythema), decreased appetite, vomiting, hyperactivity, ataxia, trembling, and behavior disorder (hiding).

In some cases death has been reported.

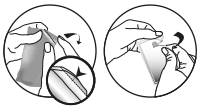
In humans, ocular and dermal irritation, nausea, numbness or tingling of the mouth and lips, anaphylaxis, pruritus, vomiting, and tongue/taste abnormalities have been reported following exposure to this product.

Contact Information:
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.

DOSAGE AND ADMINISTRATION:
The recommended minimum dose is 4.5 mg/lb (10.0 mg/kg) imidacloprid and 0.45 mg/lb (1.0 mg/kg) moxidectin, once a month, by topical administration.

Do not apply to irritated skin.

1. Remove the applicator from the outer pouch using scissors or fold along diagonal line to expose nick; tear back at nick. As specified in the following table, administer the entire contents of the *Midamox for Cats* (imidacloprid and moxidectin) applicator that correctly corresponds with the body weight of the cat.



Cat (lbs.)	*Midamox for Cats*	Volume (mL)	Imidacloprid (mg)	Moxidectin (mg)
2–5	*Midamox 5*	0.23	23	2.3
5.1–9	*Midamox 9*	0.4	40	4
9.1–18*	*Midamox 18*	0.8	80	8

* Cats over 18 lbs. should be treated with the appropriate combination of *Midamox for Cats* applicators.

2. Hold the applicator upright.
3. Tap the narrow part of the applicator to ensure the contents remain within the main body of the applicator.

4. Twist or snap back the tip.
5. Part the hair on the back of the cat's neck at the base of the head in front of the shoulder blades, until the skin is visible. Place the tip of the applicator on the skin and squeeze the applicator several times to empty its contents completely and directly onto the skin in one spot.

Do not get this product in the cat's mouth or eyes or allow the cat to lick the application site for 30 minutes. Treatment at the base of the head will minimize the opportunity for ingestion by grooming. In households with multiple pets, keep animals separated to prevent licking of the application site.

Stiff, matted hair or a damp, oily appearance of the hair may be observed at the application site on some cats. This is temporary and does not affect the safety and effectiveness of the product.

Heartworm Prevention: For prevention of heartworm disease, *Midamox for Cats* should be administered at one-month intervals. *Midamox for Cats* may be administered year-round or at a minimum should start one month before the first expected exposure to mosquitoes and should continue at monthly intervals until one month after the last exposure to mosquitoes. If a dose is missed and a 30-day interval between doses is exceeded, administer *Midamox for Cats* immediately and resume the monthly dosing schedule. When replacing another heartworm preventative product in a heartworm prevention program, the first treatment with *Midamox for Cats* should be given within one month of the last dose of the former medication. At the discretion of the veterinarian, cats older than 6 months of age may be tested to determine the presence of existing heartworm infection before treatment with *Midamox for Cats* **(See ADVERSE REACTIONS – Post-Approval Experience).**

Flea Treatment: For the treatment of flea infestations, *Midamox for Cats* should be administered at one-month intervals. If the cat is already infested with fleas when the first dose of *Midamox for Cats* is administered, adult fleas on the cat will be killed. However, re-infestation from the emergence of pre-existing pupae in the environment may continue to occur for six weeks or longer after treatment is initiated. Cats treated with imidacloprid, including those with pre-existing flea allergy dermatitis have shown clinical improvement as a direct result of elimination of fleas from the cat.

Ear Mite Treatment: For the treatment of ear mites (*Otodectes cynotis*), *Midamox for Cats* should be administered once as a single topical dose. Monthly use of *Midamox for Cats* will control any subsequent ear mite infestations.

Intestinal Nematode Treatment: For the treatment and control of intestinal hookworm infections caused by *Ancylostoma tubaeforme* (adults, immature adults and fourth stage larvae) and roundworm infections caused by *Toxocara cati* (adults and fourth stage larvae), *Midamox for Cats* should be administered once as a single topical dose.

ANIMAL SAFETY:
Studies in Kittens: Imidacloprid and moxidectin was topically applied at 0, 1, 3, and 5X the maximum dose to 48 healthy 9-week-old kittens on days 0, 28, and 56. Lethargy was observed in 1 kitten from the 3X group and 1 from the 5X group on the day after initial treatment; the kitten from the 3X group was also disoriented and ataxic. One kitten from the 3X group had a slow pupillary light response two days after treatment and one had

tremors the day after treatment. Hypersalivation was seen in one kitten from the 5X group approximately six hours post-treatment. One kitten from the 3X group was scratching at the treatment site 2 days after treatment. Slight cough was noted in 7 different kittens (2-0X, 2-1X, and 3-5X) during the 13-day period following the first treatment. Histopathology showed granulomatous inflammation at the treatment site in three 1X kittens. Causal relationship to the drug could not be determined. Pulmonary inflammation (1-5X) and lymphoid hyperplasia (2-1X, 4-3X) were seen in treated kittens. In a second study, imidacloprid and moxidectin was topically applied at 0, 1.7, 5.2 and 8.7X the maximum dose to 48 healthy 9-week-old kittens every two weeks for 6 doses. One kitten in the 8.7X group apparently ingested an unknown amount of the drug and developed the following clinical signs prior to euthanasia: mydriasis, salivation, depression, vomiting, unsteadiness, rapid to slow to difficult breathing, poor pupillary response, generalized tremors, inability to move, and nystagmus. Two kittens in the 5.2X group developed mydriasis, salivation, depression, squinting, and poor appetite. A kitten in the 1.7X group developed mydriasis.

Dose Tolerance Study: Eight healthy juvenile cats were topically dosed with a single application of imidacloprid and moxidectin at 10 times the recommended dose volume. Mild, transient hypersalivation occurred in two of the cats.

Oral Study in Cats: The oral safety of imidacloprid and moxidectin was tested in case of accidental oral ingestion. The maximum topical dose was orally administered to twelve healthy 9-week-old kittens. Hypersalivation (8 of 12 kittens) and vomiting (12 of 12 kittens) were observed immediately post-treatment. Tremors developed in one kitten within 1 hour, resolving without treatment within the next hour. All 12 kittens were either anorexic or had decreased appetite for at least 1 day following treatment. In 3 kittens, the anorexia or decreased appetite continued into the second week following treatment. There was a post-treatment loss of body weight in treated kittens compared to control kittens. In a pilot safety study using kittens younger in age and lighter in weight than allowed by product labeling, an 8-week-old kitten weighing 0.6 kg orally received 2X of the label topical dose (0.46 mL/kg). Immediately after dosing, it vomited, had labored breathing and slight tremors. Within 4 hours, it was normal, but was found dead on day 6. Necropsy could not determine the cause of death.

Study in Heartworm Positive Cats: Young adult cats were inoculated subcutaneously with third-stage *D. immitis* larvae. At 243-245 days post-infection, immunoserology and echocardiography were performed to identify cats with adult heartworm burdens similar to naturally-acquired infections. Two groups were treated topically with either imidacloprid and moxidectin at the label dose or placebo, once every 28 days, for three consecutive treatments. A third group was treated topically, once, with imidacloprid and moxidectin at 5X the label dose. Sporadic vomiting and labored breathing related to heartworm burden were observed in the treatment and control groups. There was no difference between treatment groups in the numbers of adult *D. immitis* recovered at study conclusion. No adverse reactions were associated with the topical application of imidacloprid and moxidectin to experimentally heartworm-infected cats.

FERRETS
Use only the 0.4 mL *MIDAMOX* for Cats in ferrets. The 0.23 mL size does not provide an effective dose and the 0.8 mL size could result in an overdose.

INDICATIONS:
For ferrets:
Midamox for Cats is indicated for the prevention of heartworm disease in ferrets caused by *Dirofilaria immitis*. *Midamox for Cats* kills adult fleas *(Ctenocephalides felis)* and is indicated for the treatment of flea infestations on ferrets.

WARNINGS:
Do not use on sick or debilitated ferrets.

PRECAUTIONS:
Do not dispense dose applicator tubes without complete safety and administration information.

The safety of *Midamox for Cats* has not been established in breeding, pregnant, and lactating ferrets.

Treatment of ferrets weighing less than 2.0 lbs (0.9 kg) should be based on a risk- benefit assessment.

The effectiveness of *Midamox for Cats* in ferrets weighing over 4.4 lbs (2.0 kg) has not been established.

ADVERSE REACTIONS:
Field Safety Study in Ferrets: Imidacloprid and moxidectin was topically administered to 131 client-owned ferrets at the recommended dose volume (0.4 mL). The ferrets ranged in age from 3 months to 7 years, and weighed between 0.5 and 1.86 kg (1.1 to 4.1 lbs). The dose of imidacloprid ranged between 21.5 to 80.2 mg/kg in this study. The dose of moxidectin ranged between 2.2 to 8.0 mg/kg in this study.

Adverse reactions in ferrets following treatment included: pruritus/scratching, scabbing, redness, wounds and inflammation at the treatment site; lethargy; and chemical odor. These adverse reactions resolved without additional therapy. Owners also reported stiffening of the hair at the treatment site, however, this is expected with application of a topical product and is not considered an adverse reaction.

Three human adverse reactions were reported. An owner's finger became red following skin contact with the product. One owner reported a headache caused by the chemical odor of the product. One owner reported a tingling sensation of the lips after kissing the treatment site.

Foreign Market Experience: Because the following events were reported voluntarily during post-approval use of the product in foreign markets, it is not always possible to reliably establish a causal relationship to drug exposure. Adverse events reported in ferrets topically treated with 0.4 mL imidacloprid + moxidectin for cats included: malaise, vomiting, diarrhea, shaking, mydriasis, hypersalivation with abnormal neurologic signs, seizures, death, generalized hematoma of the body, and alopecia at the treatment site. Adverse reactions in humans included: burning, tingling, numbness, bad taste in the mouth, dizziness, and headache.

ANIMAL SAFETY:
Ferrets: Imidacloprid and moxidectin was topically applied at 5X the recommended dose volume to six healthy 9-month-old ferrets on Study Days 0, 14, 28, and 42. Because the weights of the ferrets in this study ranged from 2.0 to 4.0 lb (0.9 kg to 1.8 kg), ferrets received a range of dosages from 51.0 to 106.9 mg/lb (112 to 235 mg/kg) of imidacloprid and 5 to 10.5 mg/lb (11 to 23 mg/kg) of moxidectin. The following abnormal clinical signs were reported during the study: wet, matted, and/or greasy appearance to the hair, shaking of the head and/or body, rubbing of dose site on cage, and shedding. Slight increases in phosphorous, potassium, aspartate aminotransferase (AST), and glucose were seen during the study, however, no clinical signs related to these bloodwork changes were reported.

Oral Safety Study: Imidacloprid and moxidectin was orally administered at the recommended dose volume (0.4 mL) to eight healthy ferrets on Study Day 0. Ferrets were 78 to 101 days old (11.1 to 14.4 weeks) and weighed between 1.1 to 1.8 lb (0.5 to 0.8 kg) body weight on the day of dosing, resulting in doses ranges of 22.0–36.8 mg/lb (48.3–81.0 mg/kg) imidacloprid and 2.2–3.7 mg/lb (4.8–8.0 mg/kg) moxidectin. The following abnormal clinical signs were reported immediately following oral administration of imidacloprid and moxidectin: vomiting (one ferret) and ataxia (two ferrets). All abnormalities resolved without treatment or supportive care.

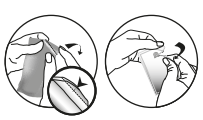
DOSAGE AND ADMINISTRATION:
For ferrets:
The recommended minimum dose for a ferret is 9 mg/lb (20 mg/kg) imidacloprid and 0.9 mg/lb (2 mg/kg) moxidectin, once a month, by topical administration.

Ferret (lbs.)	*Midamox For Cats*	Volume (mL)	Imidacloprid (mg)	Moxidectin (mg)
2.0-4.4	*Midamox 9*	0.4	40	4

Only the 0.4 mL applicator volume (*Midamox* 9) should be used on ferrets.

Do not apply to irritated skin.

1. Remove the applicator from the outer pouch using scissors or fold along diagonal line to expose nick; tear back at nick.



2. Hold the applicator upright.
3. Tap the narrow part of the applicator to ensure the contents remain within the main body of the applicator.

4. Twist or snap back the tip.
5. Part the hair on the back of the ferret's neck at the base of the head, until the skin is visible. Place the tip of the applicator on the skin and squeeze the applicator several times to empty its contents completely and directly onto the skin in one spot.

Do not get this product in the ferret's mouth or eyes or allow the ferret to lick the application site for 30 minutes. Treatment at the base of the head will minimize the opportunity for ingestion by grooming. In households with multiple pets, keep animals separated to prevent licking of the application site.
Stiff, matted hair or a damp, oily appearance of the hair may be observed at the application site on some ferrets. This is temporary and does not affect the safety or effectiveness of the product.

Heartworm Prevention: For prevention of heartworm disease, *Midamox for Cats* should be administered at one-month intervals. *Midamox for Cats* may be administered year-round or at a minimum should start one month before the first expected exposure to mosquitoes and should continue at monthly intervals until one month after the last exposure to mosquitoes. If a dose is missed and a 30-day interval between doses is exceeded, administer *Midamox for Cats* immediately and resume the monthly dosing schedule.

Flea Treatment: For the treatment of flea infestations on ferrets, *Midamox for Cats* should be administered at one-month intervals. If the ferret is already infested with fleas when the first dose of *Midamox for Cats* is administered, adult fleas on the ferret will be killed. However, re-infestation from the emergence of pre-existing pupae in the environment may continue to occur for six weeks or longer after treatment is initiated.

STORAGE INFORMATION:
Store below 77°F (25°C). Excursions are permitted up to 104°F (40°C) however such exposure should be minimized. Do not remove the applicator from the pouch until ready to use. Do not use after the expiry date which is stated on the carton.

HOW SUPPLIED:
Applications Per Package
3 x 0.23 mL applicators, 6 x 0.4 mL applicators, 6 x 0.8 mL applicators

Approved by FDA under ANADA # 200-721

Midamox® is a registered trademark of
Norbrook Laboratories Limited
Made in Ireland

Manufactured by:
Norbrook Manufacturing Ltd.
Rossmore Industrial Estate
Monaghan, Co. Monaghan
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