CARPROFEN (Veterinary—Systemic)

Some commonly used *brand names* for veterinary-labeled products are *Novox* and *Rimadyl.*

Note: For a listing of dosage forms and brand names by country availability, see the *Dosage Forms* section(s).

Category: Anti-inflammatory (nonsteroidal); analgesic; antipyretic.

Indications

Note: The text between [EL]US and [EL] describes uses that are not included in U.S. product labeling. Text between [EL]CAN and [EL] describes uses that are not included in Canadian product labeling.

The [EL]US or [EL]CAN designation can signify a lack of product availability in the country indicated. See the *Dosage Forms* section of this monograph to confirm availability.

General considerations

The relative anti-inflammatory activity of carprofen is approximately: carprofen ≈ indomethacin, piroxicam, diclofenac > phenylbutazone > ibuprofen > aspirin.{R-7} Analgesic and antipyretic activities have also been shown to be similar to indomethacin and greater than phenylbutazone or aspirin.{R-26}

Carprofen is reported to be 16 times less active than indomethacin in producing gastric ulcers in mice.{R-8; 26} Carprofen causes significantly less platelet aggregation inhibition than aspirin does; carprofen does not alter buccal mucosal bleeding time in healthy dogs when administered at recommended dosages.{R-4; 8; 53}

Accepted

Inflammation (treatment); or

Pain (treatment)—*Dogs:* Carprofen caplets, chewable tablets, and [EL]CAN injection[EL] are indicated in the control of inflammation and pain associated with osteoarthritis.{R-1; 2; 9; 40; 41; 61}

Pain, postoperative (treatment)—*Dogs:* Carprofen [EL]CAN caplets, chewable tablets[EL], and injection are indicated in the control of postoperative pain associated with soft tissue or orthopedic surgery.{R-1; 2; 61; 68}

Preoperative administration is recommended because it can be more effective than postoperative administration alone in the control of postoperative pain;{R-1; 45; 46} however, some clinicians do not recommend routine preoperative administration of NSAIDs for the control of pain. General health and age of the animal are considered in choice of analgesic, timing of administration, anesthetic regimen, and use of perioperative supportive therapy (see also *Veterinary Dosing Information* in this monograph). Preoperative carprofen administration would not be expected to significantly decrease minimum alveolar concentration of halothane or isoflurane required for anesthesia in dogs.{R-47; 48}

Potentially effective

Inflammation (treatment); or

Pain (treatment)— [EL]US,CAN *Horses*[EL]: Although the safety and efficacy have not been established, there is evidence to suggest that oral or parenteral carprofen can be effective in the treatment of pain and inflammation in horses.{R-6; 20; 27-29; 58; 59}

Regulatory Considerations

U.S. and Canada—

Carprofen is labeled for use only by or on the order of a licensed veterinarian.{R-1; 2; 40; 41} It is not labeled for use in food-producing animals.

Chemistry

Chemical group: Aryl-propionic acid class of non-steroidal anti-inflammatory drug.{R-7} The proprionic acid derivatives include ibuprofen, ketoprofen, and naproxen.{R-1}

Chemical name: 9*H*-Carbazole-2-acetic acid, 6-chloro-α-methyl-, (±)-.{R-66}

Molecular formula: $C_{15}H_{12}ClNO_2$.{R-66}

Molecular weight: 273.71.{R-66}

Description: White, crystalline compound.{R-1}

Solubility: Freely soluble in ethanol, but practically insoluble in water at 25 °C.{R-1}

Pharmacology/Pharmacokinetics

Mechanism of action/Effect: The mechanisms of action of carprofen are not completely understood. This lack of clarity may be due to species differences, to differing methodologies in the studies performed, and to the evolving understanding of anti-inflammatory activity and tests for measuring it.

Inhibition of cyclooxygenase is believed to be the mechanism of action for the anti-inflammatory effect of carprofen.{R-30; 31; 61} Research suggests carprofen selectively inhibits cyclooxygenase 2 (COX-2) over cyclooxygenase 1 (COX-1) in dogs.{R-31; 63; 64} COX-1, present in most cells and tissues, is believed to produce cytoprotective prostaglandins active in maintaining normal gastrointestinal and renal function in mammals while COX-2 produces prostaglandins involved in inflammation.{R-8} Cyclooxygenase selectivity would be expected to minimize adverse gastrointestinal and renal effects while effectively reducing inflammation. The potency of carprofen in inhibiting cyclooxygenase and its selectivity for COX-2 over COX-1 in dogs has not been consistently supported by all published research.{R-12; 63; 65} In the future, a clearer picture of anti-inflammatory mechanisms and their relationship to clinical effects may emerge.

Cyclooxygenase inhibition has also been investigated in other animal species. Carprofen has been described as a potent cyclooxygenase inhibitor in sheep, based on an *in vivo* study, but isozyme selectivity was not determined.{R-24} Carprofen inhibited cyclooxygenase in an *in vitro* study of equine blood but it did not appear to be very selective for COX-2.{R-63} *In vitro* tests of feline blood showed that carprofen may be a selective inhibitor of COX-2 in cats.{R-63}

Carprofen has been shown to inhibit the release of prostagladins from rat polymorphonuclear leucocytes, an acute inflammatory reaction, and human rheumatoid synovial cells, a chronic inflammatory reaction.{R-1}

Carprofen has also been shown to modulate humoral and cellular immune responses.{R-1}

Chirality: Carprofen contains an asymmetrical carbon atom and exists in two enantiomeric forms. Differences in pharmacokinetics and pharmacodynamics between the two enantiomers occur in animals and can also vary significantly among species.{R-13} Currently, commercially available products contain a racemic (50:50) mixture of the two enantiomers, *S*(+) and *R*(–).{R-12}

An *in vitro* study using canine cyclooxygenases showed evidence that the *S*(+)-enantiomer of carprofen is the anti-inflammatory eutomer, being more than 100 times more active against COX-2 than the *R*(–)-enantiomer.{R-31} *In vitro* studies using equine chondrocytes have demonstrated the ability of the *S*(+)-enantiomer to produce 10 to 100 times the suppression of prostaglandin E_2 production and 10 times the stimulation of proteoglycan synthesis produced by the *R*(–)-enantiomer.{R-22} In sheep, the *R*(–)-enantiomer was demonstrated *in vivo* to have little effect on prostaglandin E_2 generation in exudate, also pointing to the *S*(+)-enantiomer, equivalent to the racemic mixture in inhibiting exudate PGE_2, as the source of anti-inflammatory effect in that species.{R-24}

Plasma concentrations of the *R*(–)-enantiomer have been reported as

consistently higher than the *S*(+)-enantiomer after administration of racemic carprofen in calves, cats, cows, and horses.{R-12; 20; 21; 23; 25; 26; 28; 32} The ratio of R to S in the plasma varies by species, from as low as 1.2 in lactating dairy cows to greater than 5 in horses.{R-20; 23} In rats, the *S*(+)-enantiomer predominates in the plasma.{R-19} In dogs, one study reported the *R*(–)-enantiomer predominated in plasma while another noted no significant difference in concentrations of the R and S forms.{R-12; 37}

Conversion of one enantiomer to another does not appear to occur to any significant degree in dogs, horses, human beings, and rats; therefore, it should not affect the ratio of enantiomers in plasma.{R-12; 19; 20} Plasma concentrations of each enantiomer is not affected by concurrent administration in the racemic mixture in dogs.{R-12}

Absorption: *Dogs*—

Oral: Carprofen is rapidly and almost completely absorbed; greater than 90% bioavailability.{R-1; 10; 11}

Subcutaneous: When administered subcutaneously at a dose of about 2 mg per kg of body weight (mg/kg), carprofen has a slower rate of absorption than when administered orally. But total drug absorption in the first 12 hours after a single dose and at steady state with repeated doses is similar for the two routes of administration.{R-62}

Distribution: Racemic form does not appear to affect transfer from plasma to transudate or exudate, as demonstrated in calves and dogs; the *R*(–)-enantiomer continues to predominate.{R-12; 25} In dogs and horses, concentration of carprofen was greater in transudate and exudate in tissue cages or pouches than in plasma twenty-four to forty-eight hours after administration.{R-12; 29} However, penetration into transudate is limited until inflammation is present.{R-12; 25; 29} Penetration of carprofen into the synovial fluid of healthy joints of horses is also limited but is expected to be significantly higher with inflammation.{R-21}

Volume of distribution—Limited, considered to be constrained by high protein binding.

Calves, 8 to 10 weeks of age:

Area—

R(–)-carprofen: 0.145 ± 0.005 liters per kilogram (L/kg).{R-26}

S(+)-carprofen: 0.163 ± 0.003 L/kg.{R-26}

Steady state:

R(–)-carprofen: 0.147 ± 0.003 L/kg.{R-26}

S(+)-carprofen: 0.163 ± 0.002 L/kg.{R-26}

Calves, 16 to 17 weeks of age:

Area—

R(–)-carprofen: 0.136 ± 0.003 L/kg.{R-25}

S(+)-carprofen: 0.154 ± 0.005 L/kg.{R-25}

Steady state—

R(–)-carprofen: 0.140 ± 0.004 L/kg.{R-25}

S(+)-carprofen: 0.154 ± 0.008 L/kg.{R-25}

Cats:

Area—

Racemic mixture: 0.15 ± 0.04 L/kg;{R-32} 0.17 ± 0.09 L/kg.{R-38}

R(–)-carprofen: 0.24 ± 0.05 L/kg.{R-32}

S(+)-carprofen: 0.35 ± 0.10 L/kg.{R-32}

Steady state—Racemic mix: 0.14 ± 0.05 L/kg.{R-38}

Cows, lactating: Steady state—Racemic mix: 0.091 ± 0.003 L/kg.{R-35}

Dogs:

Area—Racemic mix: 0.18 ± 0.04 L/kg.{R-10}

Steady-state—

Racemic mix: 0.14 ± 0.02 L/kg;{R-10} 0.18 ± 0.06 L/kg.{R-11}

R(–)-carprofen: 0.12 ± 0.03 L/kg.{R-15}

S(+)-carprofen: 0.19 ± 0.05 L/kg.{R-15}

Horses:

Area—Racemic mixture: 0.23 ± 0.04 L/kg;{R-27} 0.25 ± 0.02 L/kg.{R-29}

Steady-state—

Racemic mixture: 0.22 ± 0.01 L/kg.{R-29}

R(–)-carprofen: 0.10 ± 0.01 L/kg.{R-21}

S(+)-carprofen: 0.29 ± 0.04 L/kg.{R-21}

Rats: Steady-state—

R(–)-carprofen: 0.228 ± 0.043 L/kg.{R-19}

S(+)-carprofen: 0.242 ± 0.030 L/kg.{R-19}

Sheep: Racemic mixture—

Area: 0.096 ± 0.006 L/kg.{R-33}

Steady-state: 0.093 ± 0.006 L/kg.{R-33}

Protein binding: *Dogs*—Greater than 99%.{R-1}

Half-life: Elimination—

Calves, 8 to 10 weeks of age:

R(–)-carprofen—49.7 ± 3.9 hours.{R-26}

S(+)-carprofen—37.4 ± 2.4 hours.{R-26}

Calves, 16 to 17 weeks of age:

R(–)-carprofen—37.7 ± 1.8 hours.{R-25}

S(+)-carprofen—37.4 ± 2.4 hours.{R-25}

Cats:

Racemic mix—19.4 ± 7.25 hours;{R-32} 20.0 ± 16.6 hours.{R-38}

R(–)-carprofen—21.3 ± 9.09 hours.{R-32}

S(+)-carprofen—14.6 ± 5.78 hours.{R-32}

Cows, lactating: Racemic mixture—30.7 ± 2.3 hours.{R-35}

Dogs: Racemic mixture—8.00 ± 1.18 hours;{R-10} 11.7 ± 3.05.{R-11}

Horses:

Racemic mixture—21.9 ± 2.3 hours;{R-27} 18.1 ± 1.3 hours.{R-29}

R(–)-carprofen—18.36 ± 1.02 hours;{R-20} 20.6 ± 2.55 hours.{R-21}

S(+)-carprofen—9.86 ± 1.29 hours;{R-20} 16.8 ± 1.77 hours.{R-21}

Sheep: Racemic mixture—26.1 ± 1.14 hours.{R-33}

Peak concentration: *Dogs*—

Oral administration:

Dose of approximately 2 mg/kg—Peak plasma concentration of 16.47 ± 3.95 mcg/mL at 1.05 ± 0.76 hours after administration.{R-62}

Dose of 4 mg/kg—Peak plasma concentration of 35.30 ± 2.70 mcg/mL at 1.25 ± 0.25 hours.{R-10}

Dose of approximately 7.5 mg/kg—Peak plasma concentration of 57.3 ± 9.68 mcg/mL at 0.70 ± 0.48 hour.{R-11}

Subcutaneous administration: Dose of approximately 2 mg/kg—Peak plasma concentration of 8.08 ± 1.46 mcg/mL at 2.58 ± 1.64 hours.{R-62}

Onset of action: *Dogs*—Because carprofen is absorbed more slowly when administered subcutaneously than when administered orally, onset of action may be slightly delayed in comparison.{R-61}

Duration of action: Postoperative analgesia—*Cats:* A minimum of 18 to 24 hours (as assessed by visual analogue scale) after a subcutaneous 4-mg/kg dose administered either preoperatively or at extubation.{R-54-57}

Elimination: Eliminated primarily by biotransformation, as demonstrated in dogs, horses, humans, rats, and sheep.{R-1; 15; 17; 18} In these species, both R(–)- and S(+)-enantiomers are converted to glucuronide metabolites; relative rates of enantiomer metabolism vary among species.{R-17; 20} *In vitro* testing showed the R(–)-enantiomer to be glucuronidated at a higher rate than the S(+)-enantiomer in liver microsomes of several species;{R-17} however, *in vivo* tests of horses demonstrated that glucuronidation of the

S(+)-enantiomer is favored over the R(–)-enantiomer.[R-20] Researchers have not been able to consistently link stereospecific glucuronidation rates to the differences in pharmacokinetics between enantiomers;[R-17] however, in horses, the clearly predominant S(+)-enantiomer glucuronidation may explain the higher R(–)-enantiomer concentrations in plasma samples.[R-20]

Dogs—70 to 80% of carprofen metabolites are eliminated in the feces and 10 to 20% in the urine.[R-1; 15; 18] Identified metabolites include an ester glucuronide and ether glucuronides of 2 phenolic metabolites, 7-hydroxy carprofen and 8-hydroxy carprofen.[R-1] Some enterohepatic circulation of the *S*(+)-enantiomer metabolites occurs; about 34% of the dose is recirculated.[R-17]

Human beings—Unlike rats and dogs, humans excrete most of an oral dose (65 to 70%) as ester glucuronide in the urine; the remaining drug is eliminated in the bile with subsequent enterohepatic circulation.[R-18] Neither enantiomer is favored in glucuronidation.[R-20]

Rats—In rats, biliary secretion and fecal elimination account for 60 to 75% of an intravenous dose while 20 to 30% is excreted in the urine.[R-18] In rats, the S(+)-enantiomer is predominant in the plasma while the R(–)-enantiomer is glucuronidated at a higher rate.[R-20] Less than 5% of the dose is eliminated as free, intact drug.[R-18]

Clearance—

Calves, 8 to 10 weeks of age:

R(–)-carprofen—0.035 ± 0.002 mL/min/kg.[R-26]

S(+)-carprofen—0.052 ± 0.004 mL/min/kg.[R-26]

Calves, 16 to 17 weeks of age:

R(–)-carprofen—0.042 ± 0.002 mL/min/kg.[R-25]

S(+)-carprofen—0.062 ± 0.002 mL/min/kg.[R-25]

Cats:

Racemic mix—0.10 ± 0.03 mL/min/kg;[R-32] 0.12 ± 0.05 mL/min/kg.[R-38]

R(–)-carprofen—0.13 ± 0.03 mL/min/kg.[R-32]

S(+)-carprofen—0.32 ± 0.07 mL/min/kg.[R-32]

Cows, lactating: Racemic mixture—0.04 ± 0.003 mL/min/kg.[R-25]

Dogs:

Racemic mix—0.28 ± 0.05 mL/min/kg.[R-11]

R(–)-carprofen—0.28 ± 0.07 mL/min/kg.[R-15]

S(+)-carprofen—0.47 ± 0.16 mL/min/kg.[R-15]

Horses:

Racemic mixture (as calculated from reported data): 0.10 mL/min/kg;[R-27] 0.20 mL/min/kg.[R-29]

R(–)-carprofen—0.04 ± 0.01 mL/min/kg;[R-20] 0.06 ± 0.02 mL/min/kg.[R-21]

S(+)-carprofen—0.23 ± 0.02 mL/min/kg;[R-20] 0.25 ± 0.02 mL/min/kg.[R-21]

Rats:

R(–)-carprofen—1.48 ± 0.13 mL/min/kg.[R-19]

S(+)-carprofen—0.49 ± 0.08 mL/min/kg.[R-19]

Sheep: Racemic mix—0.042 ± 0.002 mL/min/kg.[R-19]

Precautions to Consider

Pregnancy/Reproduction

Dogs—Studies have not been performed to establish the safety of carprofen in the treatment of breeding, pregnant, or lactating dogs.[R-1; 40]

Rats—Reproduction studies in rats with doses of 2, 6, or 20 mg/kg showed little evidence of teratogenicity but did demonstrate effects characteristic of prostaglandin synthetase inhibitors on parturition, including slightly prolonged gestation and a small increase in fetal deaths at birth with the highest dose.[R-36]

Lactation

Cows: Carprofen has limited distribution into milk in healthy animals. With a single low intravenous dose (0.7 mg/kg), concentration in milk has been reported to be less than 0.02 mcg/mL of milk and, with five daily doses, concentrations increased to only 0.03 mcg/mL.[R-34; 35] However, in the milk of cows with acute or induced mastitis, concentrations in milk rose to 0.164 mcg/mL within twelve hours, dropping again as the inflammation resolved.[R-34; 35]

Rats: One study suggests gastrointestinal toxicity may be increased during lactation. Eighty-five percent of the dams treated with carprofen at a dose of 20 mg/kg died during the second week of lactation, with evidence of intestinal toxicity; most pups were found alive.[R-36] Mortality rates for lactating dams were much higher than in pregnant or nonpregnant female rats.[R-36]

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Angiotensin-converting enzyme inhibitors (ACE inhibitors) or Furosemide[R-4; 7]

(because ACE inhibitors and furosemide act through the effects of vasodilatory prostaglandins on renal function, NSAIDS may decrease their effectiveness; there is not yet any evidence that this is clinically significant, but blood pressure monitoring is recommended)

Anti-inflammatory medications,[R-1] such as Corticosteroids[R-7]

Other nonsteroidal anti-inflammatory drugs[R-7]

(concurrent administration with carprofen can increase risk of toxicity, including the risk of gastrointestinal ulceration)

Nephrotoxic medications[R-1]

(could exacerbate renal effects of carprofen)

Phenobarbital[R-4; 7]

(because phenobarbital can cause elevations in liver enzymes, baseline serum chemistries should be established before beginning treatment with any NSAID)

Human drug interactions and/or related problems[R-60]

In addition to the above drug interactions reported in animals, the following drug interactions have been reported in humans, and are included in the human monograph *Anti-inflammatory Drugs, Nonsteroidal (Systemic)* in *USP DI Volume I;* these drug interactions are intended for informational purposes only and may or may not be applicable to the use of carprofen in the treatment of animals:

Note: There are no carprofen products labeled for use in human beings; the following are those listed for all systemic nonsteroidal anti-inflammatory drugs.

Anticoagulants, coumarin- or indanedione-derivative

Heparin or

Thrombolytic agents, such as:

Alteplase

Anistreplase

Streptokinase

(inhibition of platelet aggregation by nonsteroidal anti-inflammatory drugs [NSAIDs], and the possibility of NSAID-induced gastrointestinal ulceration or bleeding, may be hazardous to patients receiving anticoagulant or thrombolytic therapy)

Antidiabetic agents, oral or

Insulin

(NSAIDs may increase the hypoglycemic effect of these medications because prostaglandins are directly involved in regulatory mechanisms of glucose metabolism)

Antihypertensives, including angiotensin-converting enzyme (ACE) inhibitors, or

Diuretics

(NSAIDs may decrease the diuretic, natriuretic, and antihypertensive effects of diuretics, probably by inhibiting renal prostaglandin synthesis)
(concurrent use of an NSAID and a diuretic may increase the risk of renal failure secondary to a decrease in renal blood flow caused by inhibition of renal prostaglandin synthesis)

Cyclosporine or

Nephrotoxic medications, other
(inhibition of renal prostaglandin activity by NSAIDs may increase the plasma concentration of cyclosporine and/or the risk of cyclosporine-induced nephrotoxicity)
(the risk of adverse effects may also be increased when an NSAID is used concurrently with other nephrotoxic medications)

Digitalis glycosides
(diclofenac and ibuprofen have been shown to increase serum digoxin concentrations, and indomethacin has increased digitalis concentrations in neonates being treated for patent ductus arteriosus; the possibility should be considered that some of the other NSAIDs also may increase digoxin concentrations, leading to an increased risk of digitalis toxicity; increased monitoring and dosage adjustments of the digitalis glycoside may be necessary during and following concurrent NSAID therapy; however, studies have failed to show that flurbiprofen, ketoprofen, piroxicam, or tenoxicam increase digoxin concentrations, and phenylbutazone may decrease digitalis concentrations)

Methotrexate
(NSAIDs may decrease protein binding and/or renal elimination of methotrexate, resulting in increased and prolonged methotrexate plasma concentrations and an increased risk of toxicity, especially during high-dose methotrexate infusion therapy)

Photosensitizing medications, other
(concurrent use with photosensitizing NSAIDs may cause additive photosensitizing effects)

Platelet aggregation inhibitors, other
(concurrent use with an NSAID may increase the risk of bleeding because of additive inhibition of platelet aggregation, as well as the potential for NSAID-induced gastrointestinal ulceration or hemorrhage)
(concurrent use of sulfinpyrazone with NSAIDs may also increase the risk of gastrointestinal ulceration or hemorrhage)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

With physiology/laboratory test values

Alkaline aminotransferase (ALT [SGPT])[{R-1}] and

Alkaline phosphatase[{R-53}]
(values may be increased; see *Patient monitoring* below for more information)

Human laboratory value alterations[{R-60}]

The following laboratory value alterations have been reported in humans, and are included in the human monograph *Anti-inflammatory Drugs, Nonsteroidal (Systemic)* in *USP DI Volume I;* these laboratory value alterations are intended for informational purposes only and may or may not be applicable to the use of carprofen in the treatment of animals:

Note: There are no carprofen products labeled for use in human beings; the following are those listed for all nonsteroidal anti-inflammatory drugs (NSAIDs).

With physiology/laboratory test values

Bleeding time
(may be prolonged by many NSAIDs because of suppressed platelet aggregation)

Hematocrit or

Hemoglobin
(values may be decreased, possibly because of gastrointestinal bleeding or microbleeding and/or hemodilution caused by fluid retention)

Leukocyte count and

Platelet count
(may be decreased)

Liver function tests, including:
Alkaline phosphatase and
Lactate dehydrogenase (LDH) and
Transaminases, serum
(values may be increased; liver function test abnormalities may return to normal despite continued use; however, if significant abnormalities occur, clinical signs and symptoms consistent with liver disease develop, or systemic manifestations such as eosinophilia or rash occur, the medication should be discontinued)

Potassium, serum
(concentrations may be increased)

Renal function tests, including:
Blood urea nitrogen (BUN)
Creatinine, serum
Electrolytes, blood and urine
Urine volume
(NSAIDs may decrease renal function, resulting in increased BUN, serum creatinine, and serum electrolyte concentrations and in decreased urine volume and urine electrolyte concentrations; however, in some cases, water retention may exceed that of sodium, resulting in dilutional hyponatremia)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problems exist:

» Hypersensitivity to carprofen[{R-1}]
(a previous episode of hypersensitivity is a contraindication)

Risk-benefit should be considered when the following medical problems exist:

Bleeding disorders[{R-1}]
(the safety of carprofen in dogs with bleeding disorders, such as Von Willebrand's disease, has not been studied)
(in healthy Labrador Retrievers, carprofen administered for 5 days was shown to have no effect on buccal mucosal bleeding time; there were indications of minor changes in platelet aggregation that may have more significance when other risk factors for impaired hemostasis are present)[{R-53}]

Cardiovascular disease or

Dehydration
(animals with cardiovascular disease or dehydration can be at higher risk for renal toxicity)

Gastrointestinal disease
(may be exacerbated by carprofen administration)

Hypoproteinemia[{R-7}]
(because carprofen is highly protein bound, dosages recommended for animals with average blood protein content could produce higher free-drug concentrations in hypoproteinemic animals)

Renal disease
(occult or overt renal disease can be exacerbated by nonsteroidal anti-inflammatory drugs that inhibit prostaglandins responsible for maintaining normal organ function)[{R-1; 61}]

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; » = major clinical significance):

Alkaline aminotransferase (ALT [SGPT]) and
Alkaline phosphatase and
Aspartate aminotransferase (AST [SGOT]) and
Serum bilirubin and
Urine bilirubin

(an increase in alkaline phosphatase activity alone may occur with medications, such as carprofen, or with liver changes, as in nodular hyperplasia)[R-7]

(*for hepatoxicity*—ALT and AST provide better assessment of acute hepatoxicity than alkaline phosphatase; elevations in alkaline phosphatase can lag behind ALT and AST; an elevation of ALT that is three- to four-times normal may be an early sign of acute hepatopathy; dogs reported to have liver dysfunction in association with carprofen administration have also had bilirubinemia, bilirubinuria, and abnormal liver function tests)[R-4]

Blood chemistry, including urea nitrogen (BUN) and
Complete blood count (CBC) and
Urinalysis

(exacerbation of occult or overt chronic renal failure can occur with NSAID administration; in a few cases, acute tubular necrosis or glomerular disease has been reported) (particularly in older dogs, dogs with a history of liver or renal disease, or dogs expected to receive long-term therapy, baseline CBC and blood chemistry testing before initiation of carprofen administration and regular follow-up blood chemistry testing should be considered)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

Note: No clinically significant adverse effects were observed in dogs during investigational studies of treatment of osteoarthritis with carprofen. In field studies, reported clinical signs were similar for dogs receiving the placebo (product vehicle) control and dogs that received the labeled dose of 4.4 mg of carprofen per kg of body weight a day.[R-1] However, as with other nonsteroidal anti-inflammatory drugs (NSAIDS), adverse effects may occur in individual animals with administration of carprofen.[R-1] Side effects appear to be rare but can be serious, including death, and should be recognized as early as possible. Incidence of reported adverse events associated with carprofen administration was 0.18% in 1998 and in 1999.[R-4]

Those indicating need for medical attention

Note: Unless otherwise noted, the following are drawn from post-approval adverse drug experience reporting for dogs.

Dogs (categories listed in decreasing order of frequency)[R-1]

Gastrointestinal effects (vomiting, diarrhea, constipation, inappetence, melena, hematemesis, gastrointestinal ulceration, gastrointestinal bleeding, pancreatitis); ***hepatic effects*** (inappetence, vomiting, jaundice, acute hepatic toxicity, hepatic enzyme elevation, abnormal liver function tests, hyperbilirubinemia, bilirubinuria, hypoalbuminemia); ***neurologic effects*** (ataxia, paresis, paralysis, seizures, vestibular signs, disorientation); ***urinary effects*** (hematuria, polyuria, polydipsia, urinary incontinence, urinary tract infection, azotemia, acute renal failure, tubular abnormalities, including acute tubular necrosis, renal tubular necrosis, glucosuria, glomerular disease, including glomerulonephritis); ***behavioral effects*** (sedation, lethargy, hyperactivity, restlessness, aggressiveness); ***hematologic effects*** (immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, blood loss anemia, epistaxis); ***dermatologic effects*** (pruritis, increased shedding, alopecia, pyotraumatic moist dermatitis, necrotizing panniculitis/vasculitis, ventral ecchymosis); ***immunologic effects or hypersensitivity*** (facial swelling, hives, erythema)

Note: *Behavioral* effects associated with carprofen administration usually resolve when treatment is discontinued.

The majority of reported cases of *gastrointestinal* signs resolved with discontinuation of medication and/or treatment of underlying disease.[R-4] Gastrointestinal ulceration or perforation is reported rarely in association with carprofen administration.[R-4]

Elevated liver enzymes without clinical evidence of liver dysfunction is the most commonly reported *hepatic effect* seen in association with carprofen administration.[R-4] However, about 1.4 in 10,000 dogs treated with carprofen in 1999 were reported to develop *hepatotoxicity*, including clinical signs of liver disease, elevation of serum bilirubin, abnormal liver function tests, and histopathologic evidence of hepatic necrosis and cholestasis.[R-4; 7] Anorexia is often the first sign of hepatopathy[R-4] and the last sign to resolve, in some cases requiring 1 to 3 weeks after discontinuation of therapy.[R-39] Vomiting, icterus, lethargy, diarrhea, polydipsia, polyuria, ascites, and hematuria have also been reported with toxicosis.[R-39] See also *Patient monitoring* above in this monograph for information on laboratory tests. For dogs with hepatic dysfunction, discontinuation of carprofen therapy and immediate supportive treatment for liver disease is indicated. Severity of hepatic dysfunction and prognosis for recovery do not appear to be correlated with the dose of carprofen or length of time it was administered; these appear to be idiosyncratic reactions.[R-4]

Immune-mediated diseases, including thrombocytopenia, anemia, and skin disease have been reported in association with carprofen administration.[R-4] Thrombocytopenia and anemia are usually regenerative.[R-4]

Neurologic signs reported to be associated with carprofen administration have resolved with discontinuation of therapy.[R-4]

Pre-existing *renal* disease may be exacerbated by administration of carprofen.[R-4]

Horses

Edema, subcutaneous, temporary—with a dose of 1.4 mg/kg a day for 14 days[R-27]

Those indicating need for medical attention only if they continue or are bothersome

Incidence unkown

Dogs

Swelling and warmth at the injection site—with subcutaneous administration[R-61]

Overdose

For information in cases of overdose or unintentional ingestion, **contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center** (888-426-4435 or 900-443-0000; a fee may be required for consultation) **and/or the drug manufacturer.**

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

Note: Hepatocellular toxicosis appears to be an idiosyncratic reaction to carprofen administration rather than being clearly associated with overdosage or prolonged therapy.[R-4; 39]

Dogs

With a dose of up to 25 mg per kg of body weight (mg/kg) a day (5.7 times the labeled dose) for 13 or 52 weeks, the following

were reported:
Elevated L-alanine aminotransferase (ALT [SGPT])—with the highest dose, elevations averaged 20 IU; ***mild dermatitis***—reported as not dose-related and not clearly linked to medication{R-1}

With a dose of 22 mg/kg every twelve hours (10 times the labeled dose) or 2.2 to 11 mg/kg every twelve hours for 42 days:
Black or bloody stools—observed in 1 of 8 dogs;
hypoalbuminenia—observed in 2 of 8 dogs{R-1}

With a dose of 80 or 160 mg/kg a day for 5 days:{R-16}
Elevated L-alanine aminotransferase (ALT [SGPT]); hematocrit, decreased; hemoglobin, decreased; hemorrhagic erosions of the small intestine

Treatment of overdose

Recommended treatment consists of the following:{R-7}
- If within 4 hours of ingestion, induce emesis
- Gastric lavage
- Administer activated charcoal in a water slurry
- Supportive care, including intravenous fluids
- Administer gastric protectants
- Perform baseline blood values, including CBC and chemistry

Client Consultation

A package insert developed specifically for dog owners, the *Owner Information Sheet,* is provided by the manufacturer for clients administering oral carprofen to their dogs.{R-5}

In providing consultation, consider emphasizing the following selected information:

Counseling clients about the risks of nonsteroidal anti-inflammatory drug administration and to contact their veterinarian and discontinue medication if any of the following are observed: decreased or increased appetite; vomiting, diarrhea, or dark or tarry stools; change in water consumption; change in urination, such as increased or decreased frequency, change in color or odor; pale gums or yellowing of gums, skin, or whites of the eyes; changes in skin, such as redness, scabs, or scratching; or behavioral changes, such as decreased or increased activity, incoordination, seizure, or aggression.{R-5}

Keeping chewable tablets out of the reach of children, cats, and dogs. Cats and dogs may be attracted to the flavoring and be at risk of overdosage.{R-2}

Keeping water readily available to animals receiving carprofen to avoid dehydration.

General Dosing Information

Changing anti-inflammatory medications

Because concurrent administration of nonsteroidal anti-inflammatory drugs (NSAIDS) with corticosteroids or other NSAIDS may increase the potential for adverse effects, recommendations have been made for withdrawal or washout times for the medication being discontinued before beginning another therapy. The decision to change medication should take into account the potential for a resurgence of signs being controlled by the anti-inflammatory during the transition period.

Table 1. Washout time when switching to a(nother) NSAID{R-7}

Medication being discontinued	Minimum washout time
NSAID	48 to 72 hours
Aspirin*	10 to 14 days
Prednisone	1 week
Long-acting corticosteroid	3 to 4 weeks

*The prolonged washout time recommended for aspirin is to minimize carryover of platelet dysfunction.

For perioperative administration

Because NSAIDs can produce renal disturbances in animals prone to them, intravenous fluid therapy may be an appropriate precaution in some animals at risk for renal disease.{R-1} While young healthy dogs showed no evidence of renal dysfunction from carprofen administered before a period of anesthesia,{R-51; 52} carprofen, like other NSAIDs, may contribute to a decrease in glomerular filtration rate for up to 48 hours when administered before surgery without the benefit of intravenous fluid support.{R-49; 50}

Carprofen causes significantly less platelet aggregation inhibition than aspirin does; when administered at recommended dosages, carprofen does not alter buccal mucosal bleeding time in healthy dogs.{R-4; 8; 53} However, preoperative administration of an NSAID should be considered with caution for animals with bleeding disorders.

For treatment of adverse effects

Recommended treatment consists of the following:

For anaphylaxis
- Parenteral epinephrine.
- Oxygen administration and respiratory support.

Oral Dosage Forms

Note: The text between [EL]US[EL] and [EL] describes uses not included in U.S. product labeling. Text between [EL]CAN[EL] and [EL] describes uses that are not included in Canadian product labeling.

The [EL]US[EL] or [EL]CAN[EL] designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

CARPROFEN TABLETS

Usual dose:

Inflammation; or

Pain—*Dogs:* Oral, 4.4 mg per kg of body weight every twenty-four hours or 2.2 mg per kg of body weight every twelve hours.{R-1}

[EL]CAN[EL]Pain, postoperative[EL]—*Dogs:* Oral, 2.2 to 4.4 mg per kg of body weight, administered 2 hours prior to procedure.{R-1; 45; 46}

Note: [EL]US,CAN[EL]*Horses*—Although the safety and efficacy have not been established, an oral dose of 0.7 mg per kg of body weight a day has been recommended in the treatment of *pain* in horses.{R-27} This dose also reduces some experimental markers of inflammation, but higher dosages may be necessary in the treatment of *inflammation and pain*. A comparison of high and low doses of carprofen (4 mg/kg and 0.7 mg/kg, respectively), administered to horses with induced inflammation, demonstrated that more definitive suppression of inflammatory mediators and reduction in signs of inflammation occur with the 4-mg-per-kg dose.[EL]{R-59}

Strength(s) usually available:

U.S.—{R-1 ; 2; 67}

Veterinary-labeled product(s):

25 mg (Rx) [*Novox Caplets* (scored); *Rimadyl Caplets* (scored); *Rimadyl Chewable Tablets* (scored)].

75 mg (Rx) [*Novox Caplets* (scored*); Rimadyl Caplets* (scored); *Rimadyl Chewable Tablets* (scored)].

100 mg (Rx) [*Novox Caplets* (scored); *Rimadyl Caplets* (scored); *Rimadyl Chewable Tablets* (scored)].

Canada—{R-40; 41}

Veterinary-labeled product(s):

25 mg (Rx) [*Rimadyl Caplets* (scored); *Rimadyl Chewable Tablets* (scored)].

75 mg (Rx) [*Rimadyl Caplets* (scored); *Rimadyl Chewable Tablets* (scored)].

100 mg (Rx) [*Rimadyl Caplets* (scored); *Rimadyl Chewable Tablets* (scored)].

Packaging and storage: Store between 15 and 30 °C (59 and 86 ºF), unless otherwise specified by the manufacturer.{R-1; 2; 40; 41}

Caution: Chewable tablets should be kept out of the reach of children.{R-2} They should also be stored out of the reach of cats and dogs; they can be attracted to the flavoring and be at risk of accidental overdosage.{R-2}

USP requirements: Not in USP.

Parenteral Dosage Forms

Note: The text between [EL]US and [EL] describes uses not included in U.S. product labeling. Text between [EL]CAN and [EL] describes uses that are not included in Canadian product labeling.

The [EL]US or [EL]CAN designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

CARPROFEN INJECTION

Usual dose:

[EL]CAN Inflammation [EL]; or

[EL]CAN Pain [EL]—*Dogs:* Subcutaneous, 4.4 mg per kg of body weight every twenty-four hours or 2.2 mg per kg of body weight every twelve hours.{R-61}

Pain, postoperative—*Dogs:* Subcutaneous, 2.2 to 4.4 mg per kg of body weight, administered 2 hours prior to surgery.

The initial dose may be followed by 2.2 mg per kg of body weight every twelve hours or 4.4 mg per kg of body weight every twenty-four hours, to provide a maximum of 4.4 mg per kg of body weight within a twenty-four hour period.{R-61} In field studies, carprofen was administered for a total of three days to animals undergoing soft tissue surgery and a total of four days to animals undergoing orthopedic surgery, producing statistically significant reductions in pain scores.{R-61}

It is recommended that different sites be used when more than one injection is administered.{R-61}

Note: [EL]US,CAN *Horses*—Although the safety and efficacy have not been established, an intravenous dose of 0.7 mg per kg of body weight a day has been recommended in the treatment of *pain* in horses.{R-6; 29; 58} This dose also reduces some experimental markers of inflammation, but higher dosages may be necessary in the treatment of *inflammation and pain*. A comparison of high and low doses of carprofen (4 mg/kg and 0.7 mg/kg, respectively), administered to horses with induced inflammation, demonstrated that more definitive suppression of inflammatory mediators and reduction in signs of inflammation occur with the 4-mg-per-kg dose.[EL]{R-59}

Strength(s) usually available:

U.S.—{R-61}

Veterinary-labeled product(s):

50 mg per mL (Rx) [*Rimadyl*].

Canada—

Veterinary-labeled product(s):

50 mg per mL (Rx) [*Rimadyl*].

Packaging and storage: Store under refrigeration, between 2 and 8 °C (36 and 46 ºF),{R-61; 68} unless otherwise specified by the manufacturer.

USP requirements: Not in USP.

Developed: 2/6/04
Interim revision: 06/30/07

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