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: Carprofen® 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-propargylic derivative of 3-carboxy-5-(2-chloro-6-chloro-α-methyl-9H-carbazole-2-acetic acid. The empirical formula is C₂₆H₂₁ClNO₃S and the molecular weight is 437.32. The chemical structure of carprofen is:

\[
\text{C}_2\text{H}_1\text{ClNO}_3\text{S}
\]

Each mL of Carprofen Injection contains 50.0 mg carprofen, 30.0 mg arginine, 88.5 mg glycine hydrochloride, 169.0 mg lactose, 1.0 mg benzy alcohol, 8.17 mg sodium hydroxide, with additional sodium hydroxide and hydrochloric acid as needed to adjust the pH to 5.0.

CLINICAL PHARMACOLOGY: Carprofen is a non-narcotic, non-steroidal anti-inflammatory agent with characteristic analgesic and antipyretic activity approximately equivalent to indomethacin, in most animal models. 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. 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 specific action of particular NSAID for COX-2 versus COX-1 may vary from species to species.2 In an in vitro study using canine cell cultures, carprofen demonstrated selective inhibition of COX-2 versus COX-1.3 None of these data have 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 (in PMN) and chronic (synovial cell system) inflammatory reactions.3

Several studies have demonstrated that carprofen has modulatory effects on both hemolysis and platelet aggregation.4 Data also indicate that carprofen inhibits the production of osteclast-activating factor (OPA), PGE₃, and PGE₆ by its inhibitory effects on prostaglandin biosynthesis.5

Based upon comparison with data obtained from intravenous administration, carprofen is rapidly and nearly completely absorbed (more than 90% bioavailable) when administered orally.6 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 4.5-5.8 hours) after single oral doses varying from 1-35 mg/kg of body weight. A similar mean terminal half-life was observed for dogs, but the mean elimination half-life was approximately 11.7 hours in the dog. Carprofen is more than 95% 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 dosorocapular 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 hours after administration). 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 glucuronide of carprofen, 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: Carprofen Injection is indicated for the relief of pain and inflammation associated with osteoarthritic joint pain and postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

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


All dogs should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate tests to establish hematologic and serum biochemical baseline data prior to, and periodically during, administration of any NSAID should be considered. Owners should be advised of the 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 and hematologic toxicity. Effects may result from decreased prostaglandin production and inhibition of the enzyme cyclooxygenase which is responsible for the formation of prostaglandins in animal心血.

All NSAID formulations inhibit prostaglandin production and may cause death. When NSAIDs inhibit prostaglandins that cause inflammation they may also inhibit those prostaglandins which maintain normal homeostasis. These anti-inflammatory effects may result in clinically significant disease in patients with underlying or pre-existing disease more often than in healthy patients.11-14 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 of renal disease, or can develop 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 insult to the dogs as the carprofen is eliminated in the renal system. No renal disease is known to be associated with carprofen.

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 in nature. Signs of vomiting, diarrhea, or anorexia are the most common. Other signs of hemotoxic, neurological, renal, 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 drugs 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 manifest adverse reactions from another NSAID. Carprofen treatment was not associated with renal toxicity or gastrointestinal ulceration in well-controlled safety studies conducted in both normal and healthy dogs. As with any parenterally injected product, good hygiene procedures should be used when administering Carprofen 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 Carprofen 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. Suggested to determine the activity of carprofen when administered concurrently with other protein-bound or similarly metabolized drugs have not been conducted. Drug combinations should be monitored closely in patients requiring additional therapy. Such drugs commonly used include systemic, anticonvulsant and behavioral medications. It has been suggested that treatment with carprofen may reduce the level of inhalant anesthetic needed.15 If additional pain medication is warranted after administration of an NSAID, it is advised that opiate analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from one NSAID to another, especially switching from corticosteroid use to NSAID use.

INFORMATION FOR DOG OWNERS: Carprofene 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 tan-colored urine, increased urination, pale gums due to anemia, yellowing of gums, skin or white of the eye due to jaundice, lethargy, incoordination, seizure, or both cranial and caudal changes. Clinical signs associated with this drug class can occur without warning and in rare situations result in death (see Adverse Reactions). Owners should be advised to discontinuing Carprofene Injection therapy and contact their veterinarian immediately if signs of intolerance are observed. The most common adverse reactions experienced by patients 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 investigation of all the capril 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 for the injectable formulation. The following categories of abnormal health observations were reported. The product vehicle served as a control.

<table>
<thead>
<tr>
<th>Percentage of Dogs with Abnormal Health Observations Reported in Clinical Field Study (2 mg/kg once daily)</th>
<th>Carprofene (n=182)</th>
<th>Placebo (n=182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inappetence</td>
<td>1.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.3</td>
<td>4.4</td>
</tr>
<tr>
<td>Diarrhea/Soft stool</td>
<td>3.1</td>
<td>4.5</td>
</tr>
<tr>
<td>Behavior change</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>PUPP</td>
<td>3.7</td>
<td>4.1</td>
</tr>
<tr>
<td>SAP increase</td>
<td>7.8</td>
<td>8.3</td>
</tr>
<tr>
<td>ALT increase</td>
<td>5.4</td>
<td>4.7</td>
</tr>
<tr>
<td>AST increase</td>
<td>3.3</td>
<td>3.8</td>
</tr>
<tr>
<td>BIL increase</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Bilirubinemia</td>
<td>16.3</td>
<td>12.1</td>
</tr>
<tr>
<td>Ketonuria</td>
<td>14.7</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Clinical pathology parameters listed represent means of reports of increases from pre-treatment values; the use of clinical judgment is necessary to determine clinical relevance of laboratory changes. 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.
Based upon the blood urea nitrogen comparison between subcutaneous and oral administration, carprofen effectiveness for osteoarthritis after dosoroscapular subcutaneous and oral administration should be similar, although there may be a slight delay in the onset of relief for oral doses. Separate placebo-controlled, masked, multicenter field studies confirmed the effectiveness of carprofen injectable for the control of postoperative pain when dosed at 2 mg/kg once daily in various breeds of dogs. In these studies, the incidence of ovariectomy, cruciate repair and arthro surgeries were administered carprofen preoperatively and for a maximum of 3 days (soft tissue) or 4 days (orthopedic) postoperatively. In general, the 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/kg twice daily (1, 3, and 3 times the recommended dosage) for 42 consecutive days with no significant adverse reactions. Serum albumin for a single female dog receiving 5 mg/kg twice daily decreased to 2.1 g/dL after 2 weeks of treatment and increased to 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 treated with 1 mg/kg twice daily and in 1 dog (2 incidents) treated with 3 mg/kg twice daily. Redness of the coccyx mucosa was observed in 1 male that received 3 mg/kg twice daily.

Two of 8 dogs receiving 10 mg/kg orally twice daily (10 times the recommended total daily dose) for 14 days exhibited hypocalcemia. The mean albumin level in the dogs receiving this dose was lower (2.2 g/dL) than that of control groups (2.88 and 2.93 g/dL, respectively). Three incidents of black or bloody stool were observed in 1 dog. Five of 9 dogs exhibited reddened areas of duodenal mucosa. Histopathologic and microscopic 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 up to 11.4 mg/kg/day (5.7 times the recommended total daily dose of 2 mg/kg) of carprofen. In both studies, the drug was well tolerated clinically by all of the animals. Edema-like reactions were seen in any of the treated animals. In both studies, dogs receiving the highest doses had average increases in serum alanine aminotransferase (ALT) of approximately 200 IU/L.

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. Dosed dogs were evaluated by evaluating 1 mg/kg twice daily and 252 dogs were included in a separate study evaluating 2 mg/kg once daily. In both studies the drug was clinically well tolerated and the incidence of adverse reactions for carprofen-treated animals was no higher than placebo-treated animals (placebo contained inactive ingredients found in carprofen capsules). For animals receiving 1 mg/kg twice daily, the mean post-treatment serum ALT values were 11 IU greater and 9 IU less than pretreatment values for dogs receiving carprofen capsules and placebo, respectively. Differences were not statistically significant. For animals receiving 2 mg/kg 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 capsules 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/kg 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/kg of carprofen subcutaneously twice a week prior to surgery and once daily thereafter, as needed, for 2 days (soft tissue surgery) or 3 days (orthopedic surgery). Carprofen was administered in combination with a variety of anesthetic-related drugs. The type and severity of abnormal health observations in carprofen- and placebo-treated animals were approximately equivalent to the 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 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 1.1 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:** Carprofen Injectable is supplied in 20 mL and 50 mL amber glass, sterile, multi-dose vials.

**REFERENCES:**


To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Norbrook at 1-888-591-5777. For additional information about adverse drug events reporting or other regulatory issues, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/answermale.