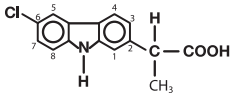
PRESCRIPTION ANIMAL REMEDY
KEEP OUT OF REACH OF CHILDREN
FOR ANIMAL TREATMENT ONLY
CARPRIEVE Injection

INDICATIONS
The active ingredient in CARPRIEVE Injection, carprofen, is a non-steroidal, anti-inflammatory drug for the control of post-operative pain and inflammation following surgery and the alleviation of pain and inflammation associated with musculo-skeletal disorders in dogs, cats and horses.

PRODUCT DESCRIPTION
CARPRIEVE Injection is a clear, sterile, mixed micelle solution for injection, containing 50 mg carprofen per mL. CARPRIEVE Injection contains carprofen, a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class. The chemical name for carprofen, a substituted carbazole, is (±)-6-chloro-∝-methylcarbazole-2-acetic acid. The structural formula is:



carprofen

Carprofen is a white, crystalline compound with an empirical formula of $C_{15}H_{12}NO_2Cl$ and a molecular weight of 273.72. 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 drug with characteristic analgesic and antipyretic activity, approximately equipotent to indomethacin in animal models[1].
As with other NSAIDs, the exact mode of action of carprofen has not been established; however, inhibition of prostaglandin synthesis accounts for at least part of its mechanism of action[2].
Carprofen is a moderately potent inhibitor of phospholipase A_2 and a reversible inhibitor of cyclooxygenase[3].
Two unique cyclooxygenases have been described in mammals[4]. The constitutive cyclooxygenase, COX-1, synthesises 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 either COX-2 or COX-1 may vary from species to species. In an *in vitro* study using canine cell cultures, carprofen demonstrated a greater than 100-fold selective inhibition of COX-2 compared with COX-1[1].
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].
In mice, carprofen has been shown to be a much weaker blocker of castor oil induced diarrhoea and arachidonic acid-induced toxicity than indomethacin[5]. This decreased effect of carprofen on prostaglandin synthesis in the gastrointestinal tract may explain its relatively low ulcerogenic activity compared to other drugs in its class[1,6].
Several studies have demonstrated that carprofen has modulatory effects on both humoral and cellular immune responses[7,8,9,10].
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].
Whole blood clotting times were evaluated in dogs given carprofen at a dose rate of 9 mg/kg once daily for 14 days. At all observations both prior to and during treatment, the mean clotting times remained within the range of normal values[11]. Based upon comparison with data obtained from intravenous administration, carprofen is rapidly and nearly completely absorbed (more than 90% bioavailable) when administered orally[11,12]. The mean terminal half-life of carprofen is approximately 8 hours (range 4.5 – 9.8 hours) after single oral doses varying from 1-25 mg/kg of bodyweight. After a 100 mg single intravenous bolus dose, the mean elimination half-life was approximately 11.7 hours in the dog[12]. Carprofen is more than 99% bound to plasma protein and exhibits a very small volume of distribution[12]. 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 faeces (70-80%) and urine (10-20%)[13]. Some enterohepatic circulation of the drug has been observed. Studies have not revealed any evidence of chiral inversion of carprofen enantiomers[14,15].

DIRECTIONS FOR USE:
Contraindications:
The stated dose and duration of treatment SHOULD NOT be exceeded. Product MUST NOT be administered by intramuscular injection. This product is contraindicated in animals exhibiting previous hypersensitivity to Carprofen. This product is contraindicated in animals suffering from cardiac, hepatic or renal disease or where there is evidence of a blood dyscrasia to the product. Its use in dehydrated, hypovolemic or hypotensive animals is associated with a potential risk of increased renal toxicity in such cases. This product is contraindicated in dogs with bleeding disorders (e.g., Von Willebrand's disease)

Precautions:
AVOID administration concurrently with other NSAIDs, steroids or potential nephrotoxic drugs. If changing anti-inflammatory products, take into account the pharmacokinetic properties of the drugs used previously when considering the delay period between the individual drugs. Studies to determine the activity of CARPRIEVE Injection when administered concurrently with other protein-bound drugs have not been conducted. Drug compatibility should be considered in patients requiring additional therapy.
The safe use of CARPRIEVE Injection in pregnant and lactating bitches and animals used for breeding purposes has not been established. In the absence of any specific studies in pregnant target animals, such use is contraindicated.
All animals should undergo a thorough clinical examination and appropriate laboratory tests to establish haematological and serum biochemical baseline data before introduction of NSAID therapy. During extended administration, appropriate re-evaluation and laboratory tests should be undertaken periodically.
Use in animals less than 6 weeks of age, or in aged animals, may involve additional risk. If such use cannot be avoided, such animals may require a reduced dosage and careful clinical management.
NSAIDs can cause inhibition of phagocytosis and hence in the treatment of inflammatory conditions associated with bacterial infection, appropriate concurrent antimicrobial therapy should be instigated.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal and renal 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. When NSAIDs inhibit prostaglandins that cause inflammation they may also inhibit those prostaglandins which maintain 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. Sensitivity to drug-associated adverse effects varies with the individual patient. NSAID therapy could unmask occult disease, which has previously been undiagnosed due to the absence of clinical signs.

ADVERSE REACTIONS:
Carprofen is an NSAID, and as with others in the class, adverse reactions may occur with its use. Typical adverse reactions of NSAIDs include loss of appetite, vomiting, diarrhoea, melaena or faecal occult blood and lethargy. Events involving suspected renal, haematological, neurological, dermatological and hepatic effects have also been reported. Symptomatic treatment may be necessary. In rare cases death has been reported. In most cases, side effects are transient and disappear following termination of treatment in dogs and cats. Owners should be advised to discontinue therapy and contact their veterinary surgeon immediately if signs of intolerance are observed.

DOSAGE AND ADMINISTRATION:
Once broached, the product is stable for use at temperatures up to 25°C for 28 days.
Dogs: For intravenous and subcutaneous use. Dose rate is 4.0 mg/kg (1 mL/12.5 kg) bodyweight. CARPRIEVE Injection is best given pre-operatively, either at the time of pre-medication or induction of anaesthesia.
Cats: For intravenous and subcutaneous use as a single dose. Dose rate is 4.0 mg/kg (0.24 mL/3.0 kg). CARPRIEVE Injection is best given pre-operatively, either at the time of pre-medication or induction of anaesthesia. The use of an insulin syringe is recommended to measure the dose accurately.
Horses: For intravenous use only. Dose rate is 0.7 mg/kg (1 mL/70 kg) bodyweight. CARPRIEVE Injection should be given by intravenous injection as a single dose. The dose may be repeated after 24 hours and then daily for a total treatment period of up to 5 days. A clinical re-evaluation should be conducted before continuing treatment beyond 5 days.

MEAT WITHHOLDING PERIOD (HORSES): DO NOT USE less than 28 days before slaughter for human consumption.

FIRST AID:
If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126.
Disposal: Dispose of empty containers or expired product by wrapping with paper and putting in garbage.
Storage: Store below 25˚C (Air conditioning). Do not refrigerate or freeze. Precipitation may occur due to cold temperature. To redissolve warm and gently agitate the vial. Protect from light. Once broached, the product is stable for use at temperatures up to 25°C for 28 days.
Presentation: CARPRIEVE Injection is available in 20 mL multi-dose amber glass vials.

Manufactured in the UK for:
Norbrook Laboratories Australia Pty Limited
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APVMA Approval Number: 56770/60666

REFERENCES:

1. Baruth H, Berger L, Bradshaw D, Cashin CH, Coffey JW, Gupta N, Konikoff J, Roberts NA and Wyler-Plaut R (1986) Carprofen. IN: Anti-Inflammatory and Anti-Rheumatic Drugs, Vol. II, Newer Anti-Inflammatory Drugs, Rainsford KD, ed. CRC Press, Boca Raton, P. 33-47.
2. Rickets AP, Lundy KM and Seibel SB (1998). Evaluation of selective inhibition of canine cyclooxygenase 1 and 2 by carprofen and other nonsteroidal anti-inflammatory drugs. Am J Vet Res 59(11):1441-6.
3. Hope WC and Welton AF (1983) Comparison of nonsteroidal anti-inflammatory drugs as inhibitors of phospholipase A2. (Abstract) Fed Proc Am Soc Exp Biol 42:875.
4. Masferrer JL, Isakson PC and Seibert K (1996) Cyclooxygenase-2 Inhibitors. A new class of anti-inflammatory agents that spare the gastrointestinal tract. Gastroenterology Clin North Am 25:363-372.
5. Strub KM and Muller RKM (1979) Relation between ulcerogenic activity of various NSAIDs and their potency as inhibitors of prostaglandin synthesis in vivo. IN: Arachidonic Acid Metabolism in Inflammation and Thrombosis. Brune K, Baggioline M, eds. Birkhauser Verlag, Basel, Pp 245-253.
6. Randall LO and Baruth H (1976) Analgesic and Anti-Inflammatory Activity of 6-Chloro-Alpha-Methyl-Carbazole-2-Acetic Acid (C-5720). Arch Int Pharmacodyn 220:94-114.
7. Ceuppens JL, Rodriguez MA and Goodwin JS (1982) Non-steroidal anti-inflammatory agents inhibit the synthesis of IgM rheumatoid factor in vitro.Lancet 1(8271):528-530.
8. Ceuppens JL and Goodwin JS (1982) Endogenous prostaglandin E2 enhances polyclonal immunoglobulin production by tonically inhibiting T suppressor cell activity. Cellular Immunology 70:41-54.
9. Schleimer RP and Benjamini E (1981) Effects of prostaglandin synthesis inhibition on the immune response.Immunopharmacology 3:205-219.
10. Veit BC (1982) Immunoregulatory activity of cultured-induced suppressor macrophages. Cellular Immunology 72:14-27.
11. McKellar QA, Pearson T, Bogan JA, Galbraith EA, Lees P, Ludwig B and Tiberghien MP (1990) Pharmacokinetics, tolerance and serum thromboxane inhibition of carprofen in the dog. Journal of Small Animal Practice 31:443-448.
12. Schmitt M and Guentert W (1990) Biopharmaceutical evaluation of carprofen following single intravenous, oral, and rectal doses in dogs. Biopharm Drug Dispos 11(7):585-594.
13. Rubio F, Seawall S, Pocelinko R, DeBarbieri B, Benz W, Berger L, Morgan L, Pao J, Williams TH and Koechlin B (1980) Metabolism of carprofen, a nonsteroidal anti-inflammatory agent, in rats, dogs, and humans. J Pharmaceutical Sciences 69:1245-1253.
14. Priymenko N, Garnier F, Ferre JP, Delatour P and Toutain PL (1998) Enantioselectivity of the enterohepatic recycling of carprofen in the dog. Drug Metab Dispos 26(2):170-6.
15. McKellar QA, Delatour P and Lees P (1994) Stereospecific pharmacodynamics and pharmacokinetics of carprofen in the dog. J Vet Pharmacol Therap 17(6):447-54.

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