



## COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

### CARPROFEN

#### SUMMARY REPORT (1)

1. Carprofen, (6-chloro-alpha-methyl-9H-carbazole-2-acetic acid) is a non-steroidal anti-inflammatory drug. It is a racemic mixture with the D-isomer being more pharmacologically active than the L-isomer. In veterinary medicine it is used in horses and cattle. In cattle the proposed dosage is 1.4 mg/kg/day as a single intravenous or subcutaneous injection. In horses the proposed dosage is 0.7 mg/kg bw/day as an intravenous injection or by oral administration for up to 10 days.
2. The general pharmacological profile of carprofen has been studied in experimental animals. Carprofen possesses strong anti-inflammatory and analgesic activities. Carprofen has a weak and competitive inhibitory effect on the activity of the prostaglandin synthetase enzyme complex; it inhibited the formation of prostaglandin E<sub>2</sub> and F<sub>2</sub> α and was found to be a weak inhibitor of arachidonate-lipoxygenase activity of human platelets.
3. Carprofen is absorbed following oral administration in all the laboratory species studied. In horses, the bioavailability of all oral preparations tested was high (75 to 100%). It is highly protein bound to plasma proteins (greater than 99% in cattle and horses).
4. In rats and dogs, Carprofen is metabolised by conjugation and oxidation. In cattle, metabolism is slow with parent compound being the major metabolite in liver, kidney and fat. In horses, the metabolic pathway proposed also involves conjugation and oxidation. The major metabolite in horses is Carprofen glucuronyl ester.
5. Pharmacokinetic studies from dogs, cattle and horses indicate that carprofen has a small volume of distribution and a slow systemic clearance. In dogs the pharmacokinetic parameters following administration of the racemate were very similar to those for each isomer alone.

The plasma elimination half-life in respect of horses and cattle is slow. The half-lives in horses after intramuscular injection was 23.7 to 43.3 hours in horses and 25.7-32.3 hours in ponies. The values of the plasma elimination half-life were significantly longer than those of other NSAID's in horses. Likewise in respect of cattle, the plasma elimination half-life of Carprofen is in the range of 44.5 to 64.6 hours. These values are longer than those reported for other NSAID's used in veterinary medicine. Age dependent pharmacokinetics are shown in calves. The elimination half life in 4 to 7 week old calves is approximately twice as long and the systemic clearance is approximately two fold lower in calves that are six weeks older.

Excretion in the dog, rat and cattle is predominantly faecal after biliary secretion but in the horse it is mainly urinary.

6. A comprehensive range of toxicity studies have been conducted on carprofen. The compound has low toxic potential following single (acute) administration. Oral LD<sub>50</sub> in mice is 282 mg/kg; oral LD<sub>50</sub> in rats is 149 mg/kg.

7. Several oral repeated dose toxicity studies were carried out in rats and in dogs. While studies were conducted in accordance with the standards of the time, they were not approved according to GLP. They were however well conducted and are adequate. In rats administered carprofen by gavage for six months, doses of up to 5 mg/kg bw/day were well tolerated without mortality or evidence of systemic toxicity. Deaths were recorded at doses of 10 mg/kg bw and above. In dogs dose levels of 2 and 7 mg carprofen/kg bw/day for up to 1 year were well tolerated with no gross autopsy or histological changes.
8. The NOEL is based on a 2 year oral toxicity study in rats, given 0, 1, 3 or 10 mg carprofen/kg bw/day in the diet. At a dose of 1 mg/kg bw/day, rats tolerated carprofen well. The 3 mg/kg/day dose level was only slightly less well tolerated with a slight increase in ulceration or peritonitis resulting from perforation of an ulcer of the small intestine. At 10 mg/kg/day there were increases in mortality, intestinal ulceration and peritonitis.
9. Segment I, II and III reproductive toxicity studies were conducted in a number of laboratory species. No teratogenic or fetotoxic effects of Carprofen were found. In some of the studies increased mortality among pups was considered to be secondary to maternal morbidity.
10. Carprofen was tested for mutagenicity in a range of tests covering the range of end-points suggested in EC guidelines: bacterial gene mutation, *in vitro* gene mutation in mammalian cells, *in vitro* clastogenicity and an *in vivo* test for somatic cell mutation. The tests for mutagenicity gave uniformly negative results.
11. A 2-year oral toxicity study has been conducted in rats and an 80 week oral carcinogenicity study has been presented in respect of mice. No carcinogenic potential for carprofen was detected in either test.
12. Carprofen was not a sensitizer in the guinea pig sensitisation test. The compound was classified as non irritating when applied to either intact or abraded skin of rabbits.
13. No data are provided on the microbiological properties of residues. However, there is no evidence from the data presented to suggest any microbiological hazard from this class of compound.
14. Carprofen has been used previously for over 10 years in human medicine at dosages of 150 to 600 mg per day. During clinical trials in humans carprofen was generally well tolerated. The majority of adverse effects were transient and mild such as gastro-intestinal discomfort or pain and nausea. The incidence of side effects in humans is similar to those recorded with aspirin and other non-steroidal anti-inflammatory drugs. Carprofen is no longer marketed for human use having been withdrawn from the market on commercial grounds.
15. No information is available on the NOEL for pharmacological effects of carprofen in humans. Furthermore, the metabolites of carprofen were not investigated for pharmacological activity. The NOEL used in the calculation of the ADI is based therefore on a toxicological study from the 24-month oral toxicity study in the rat. A safety factor of 100 is justified and the ADI established is 0.01 mg/kg.
16. Residue depletion studies were conducted in calves using radiolabelled carprofen injected subcutaneously at a dose of 1.4 mg/kg bw. The percentage of carprofen in total residue was approximately 70% on liver, kidney, muscle and fat within 3 days of dosing, dropping to 65% by 2 weeks post treatment. In older animals, both the total residue and the percentage of residue present as carprofen were lower (approximately half) at equivalent slaughter time points. Carprofen residues amounted to 48 to 80% of total residues in tissues at 8 days post treatment in these older animals. The remaining metabolites were either conjugates of carprofen or hydroxy derivatives. Depletion from muscle is rapid, however depletion from the injection site is slower, concentrations of 0.3 mg carprofen/kg tissue were present at 8 days post treatment.

Residue depletion studies were conducted in horses using radiolabelled compound at a dose level of 0.7 mg/kg bw. At 7 days post intravenous administration, radioactive residues were detectable in liver and kidney, while residues in muscle and fat were generally at or near the limit of detection. Investigation of the nature of the radioactivity 6 hours and 24 hours after intravenous administration revealed that parent compound accounted for 33%-36% of total residues in liver, 20% to 34% in kidney, 34% to 54% in muscle and 34% in fat.

17. A routine analytical method for the determination of residues of carprofen in tissues of cattle is based on HPLC. The limit of quantification in respect of all tissues is 25 µg/kg. However, the method has not been described according to the ISO 78/2 format and the specificity of the method has not been adequately demonstrated. A validated routine method for horses has not been presented.
18. Taking into account the pattern of residues depletion in horses and cattle, the following provisional MRLs are elaborated, with carprofen being the marker residue:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissue	Other provisions
Carprofen	Carprofen	Equine	1000 µg/kg 1000 µg/kg 50 µg/kg 100 µg/kg	Liver Kidney Muscle Fat	Provisional MRL expires on 01.01.98
		Bovine	1000 µg/kg 1000 µg/kg 500 µg/kg 500 µg/kg	Liver Kidney Muscle Fat	

Residues in treated animals deplete to levels below these limits within 8 days in cattle and within 4 days in horses. From the MRLs proposed for cattle the total residue ingested by a consumer would be 0.33 mg. This represents 55% of the ADI.

## LIST OF QUESTIONS

The following questions must be addressed before carprofen can be considered for inclusion into Annex I of Council Regulation (EEC) 2377/90 in respect of cattle and horses:

1. The routine analytical method proposed for cattle should be described according to ISO 78/2 or a similar international standard. While validation data are presented the method has not been described according to the ISO standard.
2. A validated routine analytical method should be presented in respect of residues of carprofen in tissues of horses.
3. While it is unlikely that animals will be treated simultaneously with carprofen and other non-steroidal anti-inflammatory drugs (NSAIDs) the routine analytical method should be capable of differentiating between Carprofen and other NSAIDs. Clarification of the specificity of the routine analytical method is necessary to differentiate between carprofen and residues of other NSAIDs commonly used in veterinary medicines intended for use in horses and cattle.