The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

EMEA/MRL/528/98-FINAL
January 1999

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CARPROFEN

SUMMARY REPORT (2)

1. Carprofen, (6-chloro-alpha-methyl-9H-carbazole-2-acetic acid) is a non-steroidal anti-inflammatory drug (NSAID) of the group of arylpropionic acid derivatives. 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 bw/day as a single intravenous or subcutaneous injection. In horses the proposed dosage is 0.7 mg/kg bw/day as an intravenous injection.

   An ADI of 0.01 mg/kg bw (i.e. 0.6 mg/person) based on a 2 years oral toxicity study in rats using a safety factor of 100 had previously been established by the Committee for Veterinary Medicinal Products.

   Currently, carprofen is included in Annex III of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Carprofen	Carprofen	Bovine	500 µg/kg 500 µg/kg 1000 µg/kg 1000 µg/kg	Muscle Fat Liver Kidney	Provisional MRL expire on 1.1.2000
		Equidae	50 µg/kg 100 µg/kg 1000 µg/kg 1000 µg/kg	Muscle Fat Liver Kidney	

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_2 and F_{2a} and was found to be a weak inhibitor of arachidonate-lipoxygenase activity of human platelets. From published data it was shown that the oral minimum effective dose was 1 mg/kg bw in rats and mice in a battery of screening tests. In dogs, carprofen administered as a racemic mixture at 4 mg/kg or as either the S(+) of R(-) isomer at 2 mg/kg did not inhibit the generation of thromboxane B_2 from blood or prostaglandin E_2 or 12-hydroxy-5,8,10,14-eicosatetrenoic acid in inflammatory exudate, suggesting that it does not act as a conventional non-steroidal anti-inflammatory drug through the inhibition of the enzyme cyclo-oxygenase. No clear oral pharmacological NOEL could be determined. Furthermore, the metabolites of carprofen were not investigated for pharmacological activity.

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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).

   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.

   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 to 32.3 hours in ponies. The values of the plasma elimination half-life were significantly longer than those of other non-steroidal anti-inflammatory drugs 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 non-steroidal anti-inflammatory drugs 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 than 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.

4. A comprehensive range of toxicity studies has been conducted on carprofen. The compound has low toxic potential following single (acute) administration. The oral LD_{50} in mice is 282 mg/kg bw and in rats 149 mg/kg bw.

5. Several oral repeated-dose toxicity studies were carried out in rats and in dogs. While studies were not in accordance with GLP they were well conducted, according to the standards of the time and they were considered 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.

   A NOEL of 1 mg/kg bw/day was established 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 bw/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 bw/day there were increases in mortality, intestinal ulceration and peritonitis.

6. Reproductive toxicity studies investigating the influence on fertility, embryo-/foetotoxicity including teratogenicity and peri- and postnatal development were conducted in a number of laboratory species. No teratogenic or foetotoxic effects of carprofen were found. In some of the studies increased mortality among pups was considered to be secondary to maternal morbidity.

7. 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.

8. 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.

9. Carprofen was not a sensitiser in the guinea pig sensitisation test. The compound was classified as non-irritating when applied to either intact or abraded skin of rabbits.

10. No data were 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.

11. Carprofen has been used previously for over 10 years in human medicine at dosages of 150 to 600 mg/day. During clinical trials in humans carprofen was generally well tolerated. The majority of adverse effects were transient and mild such as gastrointestinal 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. No information is available on the NOEL for pharmacological effects of carprofen in humans.

12. An ADI of 0.01 mg/kg bw (i.e. 0.6 mg/person) was established based on the NOEL of 1 mg/kg bw from the 2-year oral toxicity study in rats using a safety factor of 100. Although no pharmacological ADI could be derived, it was considered that the safety factor of 100 used in the calculation of the toxicological ADI would afford a sufficient margin of safety in comparison to the dosage formerly used in humans (150 to 600 mg/day).

13. Residue depletion studies were conducted in groups of 4 calves using radiolabelled carprofen injected subcutaneously at a dose of 1.4 mg/kg bw. At 3 days after the administration the following concentrations of total residues were measured: 500 µg equivalents carprofen/kg in muscle, 1580 µg equivalents carprofen/kg in fat, 1350 µg equivalents carprofen/kg in liver and 1740 µg equivalents carprofen/kg in kidney. Then the concentrations declined to 180 µg equivalents carprofen/kg in muscle, 730 µg equivalents carprofen/kg in fat, 650 µg equivalents carprofen/kg in liver and 780 µg equivalents carprofen/kg in kidney at 8 days post treatment. At the injection site, the total amounts of radioactivity were 1700 and 720 µg equivalents carprofen/kg at 8 and 14 days post treatment respectively.

14. The mean percentage of carprofen in total residue was approximately 70% in liver, 80% in kidney and muscle and 90% in fat regardless of time of slaughter. The remaining metabolites were either conjugates of carprofen or hydroxy derivatives.

15. Residue depletion studies were conducted in horses using radiolabelled compound at a dose level of 0.7 mg/kg bw. At 6 hours after the administration the following concentrations of total residues were measured: 180 µg equivalents carprofen/kg in muscle, 340 µg equivalents carprofen/kg in fat, 3420 µg equivalents carprofen/kg in liver and 4620 µg equivalents carprofen/kg in kidney. Then 96 hours after treatment the concentrations declined to 270 µg equivalents carprofen/kg in liver, 460 µg equivalents carprofen/kg in kidney, and close to 20 µg/kg in muscle and fat.

    Investigation of the nature of the radioactivity 6 hours after intravenous administration revealed that parent compound accounted for 37% of total residues in liver and 27% in kidney. No information for muscle and fat was provided.

16. A validated routine analytical method for the determination of residues of carprofen in tissues of cattle and horses based on HPLC is available and described according to the ISO 78/2 format. For bovine edible tissues, the limits of quantification are 25 µg/kg for muscle and fat and 10 µg/kg for kidney and liver. For equine edible tissues the limits of quantification are 500 µg/kg for kidney and liver, 25 µg/kg for muscle and 50 µg/kg for fat.

Conclusions and recommendation

Having considered:

- that an ADI of 0.01 mg/kg bw (i.e. 0.6 mg/person) has been established,
- that the marker residue is the parent compound in both cattle and horses,
- that the maximum residue limits have taken into account the distribution of residues of carprofen in edible tissues at 8 days after treatment in cattle and at 4 days after treatment in horses,
- the CVMP Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species,
- that a validated analytical method for residues monitoring purposes is available;

the Committee for Veterinary Medicinal Products recommends the inclusion of carprofen in Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Carprofen	Carprofen	Bovine	500 µg/kg 1000 µg/kg 1000 µg/kg 1000 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption
		Equidae	500 µg/kg 1000 µg/kg 1000 µg/kg 1000 µg/kg	Muscle Fat Liver Kidney	

Based on these MRL values, the daily intake will represent about 58% of the ADI