European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

CARPROFEN
(Extension to dairy cattle)

SUMMARY REPORT (3)

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 dosage is 1.4 mg/kg bw/day as a single intravenous or subcutaneous injection. In horses the 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 year oral toxicity study in rats using a safety factor of 100 had previously been established by the CVMP.

   Currently, carprofen is included 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	

2. An application has now been made for an extension to bovine milk to expand the use of carprofen to lactating dairy cattle. The recommended dose is the same as for non-dairy cattle, i.e. 1.4 mg/kg as a single dose either by intravenous or subcutaneous administration.

3. A milk residue depletion study was performed where ^{14}C-carprofen was administered by subcutaneous injection to 8 healthy dairy cows of which 4 were in early lactation (high yielders) and 4 in late lactation (low yielders). Milk samples were collected twice daily (at 12 hour intervals) from all animals, for 7 days following dose administration. Total residues in the milk were extremely low. The highest mean concentrations of radioactivity were detected in milk collected at 36 hours post administration (23.2 µg equivalents/kg). The maximum individual replicate was 38.18 µg/kg at this time. Mean concentrations then declined to 5.4 µg/kg at 168 hours post administration. HPLC analysis showed that no residues in any milk samples were above the limit of quantification (25µg/kg) in any animal at any time point. Radio-HPLC and LC-MS/MS analysis confirmed that the major component in milk samples at 36 and 96 hours was carprofen. Carprofen accounted for 66% of total residues. A second metabolite was identified as an acyl glucuronide conjugate of carprofen.

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4. A residue depletion study was performed in 32 lactating dairy cows following the subcutaneous or intravenous administration of carprofen at 1.4 mg/kg bw/day using a commercial formulation. Eleven of the animals were high yielders, 12 were medium and 9 were low yielders. Animals were divided into 2 groups (group 1 containing 20 animals and group 2 containing 12 animals). Group 1 animals received a single intravenous dose of 1.4 mg/kg bw and group 2 animals received a single subcutaneous dose of carprofen at 1.4 mg/kg bw/day. Milk samples were collected twice daily at approximately 12 hour intervals from all animals throughout the study for 8 milkings (96 hours). Quantification of residues was by HPLC with fluorescence detection.

   Following subcutaneous administration, the highest mean carprofen residue concentrations were below the limit of quantification (25 µg/kg) at all times. The highest concentration in any milk sample was 26.1 µg/kg (72 hours after administration). This was the only sample to exceed the limit of quantification of the analytical method.

   Following intravenous administration, milk residues were slightly higher than the subcutaneous concentrations. The highest mean carprofen concentration was 25.4 µg/kg at 12 hours post administration. Mean residues were below the limit of quantification at all subsequent milkings. Eight of the twenty samples assayed at 12 hours following treatment had carprofen concentrations exceeding the validated limit of quantification of 25 µg/kg. The highest observed value was 49.6 µg/kg. All milk concentrations were below the limit of quantification at 72 hours and beyond.

5. A routine analytical method for the determination of residues of carprofen in milk of cattle based on HPLC is available and described according to the ISO 78/2 format. The limit of quantification is 25 µg/kg. The method is validated in accordance with Volume 8 of the Rules Governing Medicinal Products in the European Community with the exception of specificity.

   While the studies relating to this extension application were being conducted, it was determined that the analytical method detected not only parent compound but also the glucuronide conjugate and that both should be included in the definition of the marker residue. The extraction process and HPLC analysis results in the conjugate being hydrolysed back to the parent substance allowing the detection and quantification of both as a single peak. There have been no changes to the method except for the recognition that it now accounts for the conjugate as well as the parent substance.

Conclusions and recommendation

Having considered:

- that an ADI of 0.01 mg/kg bw (i.e. 0.6 mg/person) has previously been established;
- total residue concentrations in bovine milk following subcutaneous administration are extremely low following treatment. In a radiolabel study on 8 cows the highest total residue concentration in the milk was 38.18 µg/kg while residues of parent compound were below the limit of quantification in all samples;
- in a residue depletion study on 12 lactating cows, residues of carprofen in milk following subcutaneous use of the product were at or below the limit of quantification of the analytical method at all times;
- in a residue depletion study on 20 lactating cows, residues of carprofen in milk following intravenous use were low and declined to below the limit of quantification of the analytical method by 24 hours post treatment;
- the validated routine analytical method detects parent substance plus glucuronide conjugate, and therefore both were retained as the marker residue for tissues;
- using the highest concentration of parent compound observed following intravenous administration (49.6 µg/kg) and adjustting for total residues (0.7) and the 1.5 litre milk consumption, the potential maximum residue consumption is 106 µg, or only 18% of the ADI.

the Committee for Medicinal Products for Veterinary Use recommends the inclusion of carprofen in Annex II of Council Regulation (EEC) No 2377/90 with regard to bovine milk in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Carprofen	Bovine	For bovine milk only

The Committee also recommends the amendment of the current entry for 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	Sum of carprofen and carprofen glucuronide conjugate	Bovine, *Equidae*	500 µg/kg 1000 µg/kg 1000 µg/kg 1000 µg/kg	Muscle Fat Liver Kidney	

Based on these MRL values and taking also into account the potential intake of residues for milk, the theoretical maximum daily intake will be equivalent to about 76% of the ADI.