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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MELOXICAM (modification for bovine)

SUMMARY REPORT (3)

1. Meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide) is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. Meloxicam is indicated for use in calves and young cattle for the treatment of acute respiratory infection in combination with appropriate antibiotic therapy to reduce clinical symptoms. The recommended dosage regimen is a single dose of 0.5 mg/kg bw administered subcutaneously or intravenously.

   An ADI of 1.25 µg/kg bw (i.e. 75 µg/person) was previously established by the Committee for Veterinary Medicinal Products (CVMP) for meloxicam by applying a safety factor of 100 to the LOEL of 0.125 mg/kg bw for effects on the gestation length in a reproductive toxicity study in Sprague Dawley rats.

   Currently, meloxicam is included in Annex III of Council Regulation (EEC) No 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Meloxicam	Meloxicam	Bovine	25 µg/kg 60 µg/kg 35 µg/kg	Muscle Liver Kidney	Provisional MRLs expire on 1.1.2000

   Following the submission of the further requested data, the CVMP recommended the inclusion of meloxicam into Annex I of Council Regulation (EEC) 2377/90 with the same MRL values as previously included in Annex III.

   An application has now been submitted for the modification of the MRLs for bovine without amending the established ADI.

2. The current MRLs are based on a residue depletion study in cattle following repeated administration of 0.7 mg/kg bw for 5 days to non-dairy cattle, which is a higher dosage regimen than the recommended one. Therefore, a new depletion study was provided, in which radiolabelled meloxicam was administered subcutaneously as a single dose of 0.5 mg/kg bw.

   ^{14}C-Meloxicam was administered subcutaneously as a 0.5% formulation to groups of 4 young cattle. The mean total radioactive residue concentrations fell from 781, 689, 42 and 138 µg equivalents/kg in liver, kidney, muscle and injection site, respectively, at 2 days after dosing, to 123, 72, lower than 10 and 35 µg equivalents/kg, respectively, at 4 days after dosing, to 242, 120, lower than 13 and 21 µg equivalents/kg, respectively, at 6 days after dosing and to 120, 48, lower than 9 and 34 µg equivalents/kg respectively at 8 days after dosing.

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Meloxicam concentrations were measured by HPLC and the mean concentrations were 570, 534, 43 and 73 µg/kg in liver, kidney, muscle and injection site, respectively, at 2 days after dosing. Then, in liver and in kidney, they fell to 28 and 29 µg/kg, respectively, at 4 days after dosing, to 54 and 56 µg/kg, respectively, at 6 days after dosing and to 22 and 25 µg/kg, respectively, at 8 days after dosing. In muscle and in the injection site the concentrations of meloxicam were, in most of the samples, either below the limit of quantification (10 µg/kg) or below the limit of detection (2 µg/kg).

Fat was not analysed in this study due to the previous decision of the CVMP not to establish an MRL for fat.

According to this study ratios of marker residue to total residues of 0.23 and 0.4 can be retained for liver and kidney, respectively, at 4 days post dose, the nearest time-point when total residues in the standard food package are expected to fall below the ADI. A ratio of 1 for muscle was determined at 2 days post dose, the values in muscle being too low at 4 days to establish such a ratio.

3. A routine analytical method based on HPLC for determination of meloxicam was presented in the ISO 78/2 format and validated for muscle, liver and kidney. The limit of quantification is 10 µg/kg for all target tissues. The limits of detection are 2 µg/kg for muscle, 3 µg/kg for liver and 1.5 µg/kg for kidney.

Conclusions and recommendation

Having considered that:

- a toxicological ADI of 1.25 µg/kg bw (i.e. 75 µg/person) was previously established for meloxicam,
- meloxicam was identified as the marker residue,
- the ratio of marker residue to total residues is 1 for muscle, 0.23 for liver and 0.4 for kidney,
- a validated routine analytical method is available for monitoring residues in muscle, liver and kidney;

the Committee recommends the modification of the current entry of meloxicam 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
Meloxicam	Meloxicam	Bovine	20 µg/kg 65 µg/kg 65 µg/kg	Muscle Liver Kidney	

Based on these MRL values, the daily intake will represent approximately 57% of the ADI.