The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Information Technology

EMEA/MRL/765/00-FINAL
December 2000

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MELOXICAM
(Extension to pigs)

SUMMARY REPORT (5)

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. At present meloxicam is used in 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.

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

   Meloxicam is currently 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
Meloxicam	Meloxicam	Bovine	20 µg/kg 65 µg/kg 65 µg/kg 15 µg/kg	Muscle Liver Kidney Milk	

   An application has now been submitted for the extension of the MRLs for meloxicam to edible tissues of swine. The indication for swine is alleviation of inflammatory conditions (e.g. locomotor disorders, mastitis, metritis and agalactia syndrome) in combination with appropriate antibiotic therapy. The recommended therapeutic dose is one daily administration of 0.4 mg meloxicam/kg bw by the intramuscular route for up to 2 consecutive days.

2. The metabolism and excretion of meloxicam was investigated in mini-pigs after oral (3.5 and 10 mg/kg) and intravenous administration (10 mg/kg) of ^{14}C-meloxicam in two non-GLP studies. Meloxicam was found to be highly bound to plasma proteins (about 96%) and the concentrations in blood were found to decline with an elimination half-life of approximately 6 hours. Excretion was equally divided between urine and faeces and the majority of the excreted dose was recovered within 2 to 3 days. Meloxicam was extensively metabolised in mini-pigs and the metabolite profile was qualitatively similar in plasma and excreta. In urine less than 3% of a dose was excreted as unchanged meloxicam. In faeces meloxicam accounted for 17% of the radioactivity from orally dosed mini-pigs, but was not detected in intravenously dosed animals. A large proportion (60 to 80%) of the plasma radioactivity was unchanged meloxicam. The major metabolites found in plasma, urine and faeces were the 5-hydroxymethyl and the 5-carboxy-metabolites. Four hours after the oral dose of 3.5 mg ^{14}C-meloxicam the highest concentrations in edible tissues were found in liver and kidney. The concentration in liver was about 20 times higher than that of muscle.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 47
E-mail: mail@emea.eudra.org http://www.eudra.org/emea.html

3. A GLP compliant metabolism and residue study was performed in pigs. Sixteen pigs (Large White Hybrids, bodyweight 46.5 to 68.5 kg, 5 months of age) received an intramuscular injection of 0.4 mg ^{14}C-meloxicam/kg bw once daily for 2 consecutive days. The animals were slaughtered in groups of 2 females and 2 males at 4 hours and at 2, 4, and 8 days after the second dose. At slaughter, samples of liver, kidneys, skeletal muscle, fat (renal and omental) and muscle and skin + fat from the two injection sites were taken for analysis of total radioactivity by liquid scintillation counting. The concentrations of the parent compound meloxicam were determined using an HPLC method with LC-MS/MS detection.

   Urine and faeces were collected from 4 pigs during the dosing period and up to 4 days post last dose. Metabolite profiles were obtained in selected samples of urine, faeces and tissues by HPLC and TLC. In plasma, concentrations of radioactivity were determined up to 96 hours following the second dose by LSC and concentrations of meloxicam were determined by HPLC.

   Approximately 39% and 45% of the administered radioactivity was excreted in urine and faeces, respectively. Parent compound was only a minor component and accounted for 2.5% and 2.8% of the urinary and faecal radioactivity, respectively. The major urinary metabolites were the 5-carboxy and 5-hydroxymethyl metabolites accounting for 20 to 33% and 31 to 43% respectively in urine 24 hours after the second dose. A polar metabolite accounted for 12 to 16% but was not identified. Four other unknown metabolites were separated and represented less than 10% of the urinary radioactivity.

   The major faecal metabolite excreted during 5 days was the 5-carboxy metabolite, which accounted for approximately 65% of the faecal radioactivity.

   The major component detected in all tissue extracts from the 4-hour sacrifice corresponded to unchanged meloxicam (36 to 52%) except for liver where it was the polar metabolite. In liver meloxicam accounted for 17% of the radioactivity and the polar metabolite accounted for 37%. Low levels (1 to 8%) of radioactive components corresponding to the 5-carboxy- and 5-hydroxymethyl metabolites were also detected in most tissues. In the liver and kidney extracts from samples obtained at the 2- and 4-day sacrifices, no meloxicam was detected.

   The metabolism in the pig is qualitatively similar to rats, mini-pigs, humans and cattle although quantitatively there are differences. The major metabolites found in all species were the 5-hydroxy- and 5-carboxy-metabolites.

   Plasma radioactivity concentrations increased to a maximum mean concentration of 1662 ng equivalents/ml at 1 hour after the second dose and then declined to a mean concentration of 19 ng equivalents/ml at 96 hours post dose. Pharmacokinetic analysis revealed a C_{max} of 1730 ng equivalents/ml and a t_{max} of 1 hour.

   The concentrations of meloxicam in plasma after the second dose increased to a maximum mean concentration of 1856 ng/ml at 1 hour and thereafter declined to reach a mean concentration of 156 ng/ml at 12 hours post dose. Meloxicam was not detected in the plasma of three of the four animals beyond 12 hours post dose and was not detected in any animal beyond 24 hours post dose. Pharmacokinetic analysis revealed a C_{max} of 1885 ng/ml at 1 hour after the second dose. The elimination was rapid and the terminal half-life was estimated to 2.5 hours.

4. The pharmacokinetic study in pigs (16 animals receiving an intramuscular injection of 0.4 mg ^{14}C-meloxicam/kg bw once daily for 2 consecutive days) provided data on tissue residues up to 8 days post dose. Concentrations of radioactivity in edible tissues were highest in liver and kidney at each slaughter time. The mean total radioactive residue concentrations fell from 999 and 1450 µg equivalents/kg in liver and kidney, respectively, at 4 hour after last dose, to 175 and 105 µg equivalents/kg, respectively, at 2 days after last dose, to 91.1 and 63.6 µg equivalents/kg 4 days after last dose and to 44.8 and 20.5 µg equivalents/kg at 8 days after last dose. Levels of radioactivity in muscle were low, 55.6 and 7.6 µg equivalents/kg at 4 hour and 2 days, respectively. No radioactive residues could be detected at later time-points. Levels of radioactivity in fat and skin + fat were only detected at the 4-hour sacrifice time, 189 and 118 µg equivalents/kg, respectively.

Concentrations of meloxicam in edible tissues above the limit of quantification (10 µg/kg) were only detected at 4 hour after slaughter except in a few samples of injection sites. The mean concentrations were 446, 845, 37.6, 77.7 and 83 µg/kg in liver, kidney, muscle, fat and skin+fat, respectively.

Ratios of meloxicam to total radioactive residues could only be calculated at 4 hours post dose as no significant meloxicam residues were detected at later time-points. Ratios of meloxicam to total residues were 0.44, 0.56, 0.67, 0.42 and 0.70 in liver, kidney, muscle, fat and skin+fat, respectively.

Although liver and kidney are the major target tissues and should be assigned MRLs, for residue surveillance purposes an MRL has to be established for a tissue in the carcass. An MRL for muscle can be set at twice the limit of quantification of the analytical method in accordance with the MRLs previously established for bovine. In fat, the marker residue concentration could only be measured up to 4 hours after the last treatment, and the contribution of total daily residues was negligible after 2 days (less than 1 µg).

5. A routine analytical method based on HPLC with LC-MS/MS detection for determination of meloxicam in porcine tissues was presented in the ISO 78/2 format and validated according to Volume VI of the Rules Governing Medicinal Products in the European Community. The limit of quantification was 10 µg/kg for all porcine edible tissues and the limit of detection was 5.7 µg/kg for muscle, 1.8 µg/kg for liver, 2.0 µg/kg for kidney, 2.2 µg/kg for skin/fat and 3.0 µg/kg for fat.

Conclusions and recommendation

Having considered that:

- a toxicological ADI of 1.25 µg/kg bw (75 µg/person) was previously established for meloxicam,
- meloxicam is the marker residue,
- liver, kidney and muscle are the target tissues,
- the ratio of marker residue to total residues can be set to 0.44 for liver, 0.56 for kidney and 0.67 for muscle,
- an MRL for skin + fat was not elaborated as residue concentrations in this tissue were considered too low and of minor significance to the daily residue intake,
- a validated routine analytical method for monitoring residues of meloxicam in porcine edible tissues is available;

the Committee recommends the inclusion of meloxicam into 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	Porcine	20 µg/kg 65 µg/kg 65 µg/kg	Muscle Liver Kidney	

Based on the above MRL values, the daily intake will represent approximately 80% of the ADI.