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

EMEA/MRL/635/99-FINAL
July 1999

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MELOXICAM (extension to bovine milk)

SUMMARY REPORT (4)

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 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 . In consideration of an application for the modification of the MRLs for meloxicam, CVMP subsequently proposed the modification of the Annex I recommendation for meloxicam 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	

   An application has now been submitted for an extension to bovine milk in relation with the treatment of mastitis in dairy cows. The recommended dose is the same as for non-dairy cattle, i.e. 0.5 mg/kg bw subcutaneously or intravenously given as a single dose.

2. A milk residue depletion study was performed where ^{14}C-meloxicam was administered subcutaneously at the recommended dose regimen as a 2% formulation to 8 lactating cows (4 low milk yield and 4 high milk yield). Milk was collected twice daily, once in the morning and once in the afternoon after an interval of approximately 6 hours, for 10 days.

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Blood samples were also taken and the plasma concentration profile showed that maximum concentration of meloxicam was reached approximately 4 hours after treatment. The mean peak plasma concentrations were 2875 µg/l for low milk yield cows and 2495 µg/l for high milk yield cows. The plasma half-life of meloxicam was approximately 17.5 hours. The pharmacokinetic profile of meloxicam in lactating cows was similar to that of non-dairy cattle.

The metabolism of meloxicam was similar in low and high yield cows. Meloxicam accounted for approximately 80% of the radioactivity in milk. Two other components were also detected, the sodium salt of the oxoacetic acid moiety of meloxicam and 4-hydroxy-N-(5-hydroxymethyl)-2-thiazolyl)-2-methyl-2H-1,2-benzothiazin-3-carboxamide-1,1-dioxide. 4-Hydroxy-N-(5-hydroxy-methyl)-2-thiazolyl)-2-methyl-2H-1,2-benzothiazin-3-carboxamide-1,1-dioxide was the major metabolite accounting for 10 to 20% of the radioactivity. The sodium salt of the oxoacetic acid moiety of meloxicam was a minor component accounting for approximately 1% of the radioactivity. Both metabolites found in milk were seen in non-lactating cattle, rats and humans.

The highest mean concentrations of radioactivity were detected in milk collected at 6 hours post-dose (low milk yield, 374 µg equivalents/kg; high milk yield, 394 µg equivalents/kg). The corresponding mean concentrations of meloxicam measured by HPLC were 347 µg/kg and 325 µg/kg, respectively. Mean concentrations of radioactivity then declined to 17 µg equivalents/kg (low yield) and 15 µg equivalents/kg (high yield) at the day 5 morning milking with corresponding mean meloxicam concentrations of 13 µg/kg and 10 µg/kg, respectively. Concentrations of radioactivity were at or below the limit of detection of 1 µg/kg in all animals at the day 9 morning milking and the mean concentrations of meloxicam at the same time-point were below the limit of quantification of 2.5 µg/kg. Mean concentrations of meloxicam in the afternoon milk samples declined with half-lives of 26.5 and 21.7 hours in the high and low yield animals, respectively.

In most milk samples the proportions of meloxicam collected up to 7 days were higher than or equal to 75% of the total radioactive residues and a ratio of 0.75 can be used for the calculation of the MRL in milk.

3. A routine analytical method based on HPLC for determination of meloxicam in milk 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 2.5 µg/kg and the limit of detection was 1.5 µg/kg.

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 0.75 for milk,
- a validated routine analytical method is available for monitoring residues in milk;

the Committee recommends the inclusion of meloxicam for bovine milk 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	Bovine	15 µg/kg	Milk	

Based on the above MRL, the daily intake of meloxicam from residues in milk and bovine tissues will represent about 97% of the ADI.