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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MELOXICAM
(extension to horses)

SUMMARY REPORT (6)

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 belonging to the group of enolic acids. At present meloxicam is used in cattle for the treatment of acute respiratory infection in combination with appropriate antibiotic therapy to reduce clinical symptoms and for the treatment of diarrhoea in combination with oral rehydration therapy and in swine for alleviation of inflammatory conditions (e.g. locomotor disorders, mastitis, metritis and agalactia syndrome) in combination with appropriate antibiotic therapy. A single dose of 0.5 mg/kg bw by the intravenous or the subcutaneous route is indicated for bovines, whilst a dose of 0.4 mg meloxicam/kg bw/day intramuscularly for up to two consecutive days is recommended for swine.

   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	
		Porcine	20 µg/kg 65 µg/kg 65 µg/kg	Muscle Liver Kidney	

   An application has now been submitted for the extension of the MRLs for meloxicam to horses. The proposed indication for the horse is reduction of inflammation and relief of pain associated with both chronic musculoskeletal disorders and soft tissue lesions. The proposed recommended dose regimen is one daily administration of 0.6 mg meloxicam/kg bw/day by the oral route for a maximum of 14 days.

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2. A GLP compliant pharmacokinetic study was performed in horses after a single oral (fasted and fed horses) or intravenous administration of 0.6 mg meloxicam/kg bw. After intravenous administration the plasma clearance was estimated to 0.034 L/kg/h, the volume of distribution 0.12 l/kg and the terminal half life 8.54 hours. The oral bioavailability was high in fasted (85.3%) as well as fed horses (95.9%) and not statistically different from each other. The maximal plasma concentration was significantly lower in fed (1727 µg/l) than in fasted (2577 µg/l) animals. The mean residence time, the mean absorption time and the time to maximal plasma concentration were significantly higher in fed (9.30, 5.71 and 3.4 hours respectively) than in fasted (7.22, 3.62 and 1.5 hours respectively) horses. These data indicates that the absorption of meloxicam is slower in the presence of food although the absolute bioavailability is similar.

   In the same study, horses were administered meloxicam orally once daily for 14 consecutive days at a dose level of 0.6 mg/kg bw/day. The plasma concentrations obtained over the 14 days of administration fitted a two-compartment model. The calculated terminal half-life was 7.76 hours and the bioavailability was 97.6 %. An accumulation factor of 1.08 was calculated indicating no accumulation of meloxicam with repeated dosing. Urinary meloxicam concentrations remained fairly constant from day 0 up to day 13 of administration and declined below the limit of quantification (20 ng/ml) within 3 days after the final dose.

   The metabolism of meloxicam in horses has not been investigated.

3. A GLP compliant non-radiolabelled residue depletion study was performed in horses treated orally with 0.6 mg meloxicam/kg bw/day, once daily for 14 consecutive days. The doses were administered in the food. Groups of 4 animals per time point were slaughtered at 12, 24 and 48 hours after the last dose. Concentrations of meloxicam in muscle, liver and kidney were assayed by an HPLC method. The mean concentrations of meloxicam at 12 hours after the last dose were 115, 1280 and 18.2 µg/kg for liver, kidney and muscle, respectively. The corresponding values at 24 hours after the last dose were 58.2, 520 and less than the limit of quantification of 10 µg/kg. At 48 hours after the last dose, the mean meloxicam concentrations had declined further to less than the limit of quantification of 20 µg/kg, 56.3 µg/kg and less than the limit of detection of 3.3 µg/kg for liver, kidney and muscle, respectively. The residue depletion was similar to that in pigs.

   The non-radiolabelled residue depletion study shows that meloxicam does exist in the edible tissues of the horse and can be used as the marker residue. However, as no radiolabelled study was performed in horses the ratio of marker residue to total residues cannot be estimated.

4. Although the metabolism is not known in the horse and the ratio of marker residue to total residues cannot be calculated, it is possible to establish MRLs for meloxicam in the minor species horse. In accordance with the Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species (EMEA/CVMP/153a/97-FINAL) and the Note for Guidance on the Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMEA/CVMP/187/00-FINAL) the same MRLs can be established for the minor species Equidae as for the major species bovine and porcine.

5. The proposed routine analytical method for the determination of meloxicam in horse tissues was based on HPLC using UV for detection and presented in the ISO 78/2 format. The method, based on the fully validated method for bovine tissues, meets the requirements of Volume 8 of the Rules Governing Medicinal Products in the European Community regarding minor species. The limit of quantification was 10 µg/kg for muscle, 20 µg/kg for liver and 30 µg/kg for kidney. The limit of detection was 3.3 µg/kg for muscle, 13.2 µg/kg for liver and 12.9 µg/kg for kidney.

Conclusions and recommendation

Having considered:

- that a toxicological ADI of 1.25 µg/kg bw (75 µg/person) was previously established for meloxicam,
- that meloxicam was retained as the marker residue,
- that horse is a minor species,
- that MRLs have been established for the major species bovine and porcine,
- a routine analytical method is available for monitoring residues in the horse tissues muscle, liver and kidney;

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	*Equidae*	20 µg/kg 65 µg/kg 65 µg/kg	Muscle Liver Kidney	

Based on the above MRL values, the daily intake from tissues and bovine milk will represent less than 100% of the ADI.