The European Agency for the Evaluation of Medicinal Products

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MELOXICAM

SUMMARY REPORT (2)

1. Meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide) is a non-stereoidal anti-inflammatory drug (NSAID) belonging to the group of enolic acids. Meloxicam is indicated as adjunctive therapy in combination with antibiotic therapy, for the prevention or moderation of acute primary or secondary clinical symptoms associated with bovine respiratory infections. The substance is intended to be administered intravenously or subcutaneously in non-lactating cattle in single doses of 0.5 mg/kg bw.

   Currently, meloxicam is included in Annex III 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	25 µg/kg 60 µg/kg 35 µg/kg	Muscle Liver Kidney	Provisional MRLs expire on 1.1.2000

   The information requested for the establishment of final MRLs for meloxicam has now been provided.

2. Meloxicam inhibits the synthesis of prostaglandin E2 by inhibiting the constitutive cyclo-oxygenase effects: meloxicam has anti-inflammatory, anti-pyretic and analgesic properties and the inducible cyclooxygenase. Compared to several other NSAIDs tested meloxicam was shown to be the most selective inhibitor of inducible cyclo-oxygenase activity.

   Primary pharmacological in several species including humans, probably due to inhibition of inducible cyclooxygenase. Water-soluble forms of meloxicam showed identical pharmacological activity but were in most cases slightly more potent than meloxicam. Meloxicam had no effect on hexobarbitone sleeping time in mice. Furthermore, meloxicam had minor or no effects on the cardiovascular and respiratory systems in anesthetized cats and dogs as well as conscious dogs and in the guinea pig Langendorff preparation. Meloxicam had no anticonvulsant activity and did not affect the motility sensory function or reflexes in mice.

   Secondary pharmacological effects: the main side-effects of meloxicam are ulcerogenic activity in the gastro-intestinal tract, nephrotoxicity and disturbances of reproduction, probably due to inhibition of constitutive cyclo-oxygenase. Treatment of rats with meloxicam was associated with minor reductions in urine volume, urine sodium and a marked increase in uric acid excretion as well as an increase in urinary potassium.

3. The three main metabolites (5-hydroxymethyl-, 5-carboxy- and oxalyl-metabolite) of meloxicam found in rats and humans, showed negligible activity when tested for anti-inflammatory activity and cyclooxygenase inhibition.

4. Pharmacokinetic studies were conducted in rats, mice, dogs, mini-pigs (intravenous and/or orally, single and repeated dosing) and the target animal cattle (single dose of 0.5 mg/kg bw intravenously and subcutaneously to calves and repeated dosing of 0.7 mg/kg bw for 5 days to calves) with unlabelled or ^{14}C-labelled meloxicam.

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Meloxicam was well absorbed after oral administration in mice and dogs, with the oral bioavailability being at least 70% in mice and 100% in dogs. In calves the availability after subcutaneous administration was variable with a calculated mean of 92% compared to intravenous administration. Drug concentrations in blood were found to decline with elimination half-lives of approximately 4 to 6 hours in mice and mini-pigs, 20 to 58 hours in rats and dogs and 24 to 28 hours in calves. Extensive oral absorption and bioavailability and a relatively long half life, resembling that found in rats and dogs, have also been found for meloxicam in humans.

5. Sex and strain differences in the pharmacokinetics of meloxicam were found in rats. Thus blood drug concentrations in female rats were 2 to 4 times greater than those in males after a single dose and at steady-state. A longer drug half-life was also observed in female (38 to 58 hours) than in male rats (13 to 36 hours), and excretion in females was slower. Evidence for a similar sex difference was neither found in other laboratory species tested nor in the target species.

   Blood drug levels in pigmented animals were 6 to 10 times lower than in albino rats, C_{max} was attained much more rapidly (0.5 to 1 hours) and drug excretion was also more rapid in pigmented than in non-pigmented rats.

6. Autoradiography and measurement of the total radioactivity showed that meloxicam was distributed to all tissues in the rat and penetrated the central nervous system (small amounts), muscle layers and inflamed joints. There was no evidence for retention or accumulation in any tissues including pigmented tissues after single or repeated dosing.

   Meloxicam crossed the placenta of pregnant rats and was detected in foetal tissue at levels similar to those found in the placenta, which remained below plasma drug levels. Meloxicam and/or metabolites were excreted in rat milk, with levels in milk increasing relative to those in plasma over 1 to 24 hours after dosing. In the single dose study as well as in the repeated-dose study in calves, the highest concentrations of radioactivity were in liver, followed by kidney and bile (single dose study) at all sacrifice time points (up to 8 days). Comparatively low concentrations were found in skeletal muscle and fat.

7. Meloxicam was found to be highly bound to plasma proteins in rats (greater than 99%), mice, dogs and mini-pigs (greater than 96%). In calves plasma protein binding was found to be greater than 96.5% *ex vivo* and greater than 98% *in vitro*.

8. Radiolabelled meloxicam was found to be excreted in both urine and faeces. Excretion was predominantly via urine in rats and mice (approximately 65 to 70% of the dose) and equally divided between urine and faeces in humans, mini-pigs and cattle. There were no differences in drug excretion after oral or intravenous dosing, and minor differences in drug excretion with repeated dosing in mini-pigs and rats. The majority of the excreted dose was recovered within 2 to 3 days after treatment in mice, mini-pigs and cattle (after the last dose in the repeated dose study) and within 1 to 4 days in rats.

9. Meloxicam is extensively metabolised in rats, mice, mini-pigs, humans and cattle and the metabolite profile in plasma and excreta is qualitatively similar in rats, mini-pigs and cattle (including edible tissues). In urine less than 10% of a dose was excreted as unchanged meloxicam. The major metabolites found in all species were the 5'-hydroxy methyl- (10 to 50% of radioactivity) and 5'-carboxy- (4 to 35% of radioactivity) metabolites. The oxalyl metabolite was found in humans (30 to 35%), rats (25 to 30%) and cattle (4 to 10%), but not in mini-pigs and mice. A highly polar metabolite was found in cattle urine, but not in urine from the other species. Repeated administration of meloxicam produced no qualitative changes of metabolism compared to single administration. Rat milk contained 20% higher levels of metabolites than plasma. Studies with the 5'-hydroxymethyl and the 5'-carboxy metabolites in rats indicate a rapid excretion with the major portion of both compounds eliminated within 1 to 2 hours.

10. The acute oral toxicity for meloxicam has been investigated in rats (strains: Sprague Dawley and Chbb:THOM), minipigs, mice and rabbits. For Sprague Dawley rats the oral LD_{50} was greater than 200 mg/kg bw and 98.4 mg/kg bw for males and females, respectively. For Chbb:THOM rats the oral LD_{50} was 83.5 mg/kg bw (females and males together). In mini-pigs the oral LD_{50} was approximately 1600 mg/kg bw, in mice 470 mg/kg bw and in rabbits 320 mg/kg bw.

11. Repeated-dose toxicity was evaluated in three strains of rats (Chbb:THOM, Sprague Dawley and Wistar (intravenously: 4 weeks, orally: 4, 13, 26, 52, 78 weeks)), mice (orally: 13 weeks), micro- and mini-pigs (intravenously: 4 and 5 weeks and orally: 13 and 52 weeks). Shorter term tolerance studies were also performed in dogs (orally: 3 and 4 weeks). Doses in rats, mice, pigs and dogs were in the dose range of 0.2 to 10 mg/kg bw, 8 to 35 mg/kg bw, 1 to 10 mg/kg bw and 0.1 to 1.2 mg/kg bw, respectively. The primary target organs for toxicity were the gastrointestinal tract and kidneys. Deaths during treatment with meloxicam were associated with gastric and renal toxicity. Gastrointestinal lesions consisted of ulcers, particularly in the pyloric region of the stomach, but also in the duodenum and in some animals further along the small intestine, coagulated blood in gastrointestinal tract, peritonitis, gastric erosion, gastric dilation and/or callous thickening. Renal changes consisted of scarring, granular surface, presence of gritty concrement, necrosis and pyelonephritis. Organ weight analysis revealed weight increases of the spleen and kidneys. Once the treatment ceased the severity of toxicity and extent of reversibility were dependent on dose and duration of treatment. Female rats were more severely affected than male rats, consistent with higher blood levels of meloxicam in females compared to males. The sex difference in sensitivity was not observed in mini-pigs and mice.

    In rats the oral NOEL could be established to 0.2 mg/kg bw, in the 52-week feeding study in Wistar rats as well as after intravenous treatment for 4 weeks in Chbb:THOM rats. Minipigs were relatively insensitive to meloxicam with a NOEL of 1 mg/kg bw derived from a 13 weeks and a 52 weeks study following oral administration. In dogs a NOEL of 0.4 mg/kg was determined in the 4-week study. However, in the 3-week study occult blood was observed even in the lowest dose (0.4 mg/kg bw) and a NOEL could not be determined.

12. Tolerance studies have been performed in cattle. Meloxicam was administrated in doses of 0.5 to 1.5 mg/kg bw intravenously in calves for 5 days. Meloxicam was well tolerated in calves at the doses tested.

13. Reproductive toxicity studies in Sprague Dawley rats cover all stages of the reproduction cycle, segments I to III but the segments were performed separately and with different dosage regimes. Treatment with meloxicam was associated with reduced implantations, increases in resorption rate, prolonged pregnancy and decreased pup viability. A segment I study (doses in males: 0, 1, 2.5 and 9 mg/kg/day 9 weeks prior to mating and 3 weeks during mating, in females: 0, 1, 2.5 and 5 mg/kg bw/day 2 weeks prior to mating until day 7 of pregnancy) resulted in a dose-dependent reduction in implantation rate and increased resorption rate. Fertility indices were unaffected. In the segment II study dosing was 1 to 4 mg/kg bw during the organogenesis (day 7 to 17 of pregnancy). In this study prolongation of pregnancy and increases in foetal deaths (stillbirths) in the treated groups were observed. In a segment III study (0, 0.125, 0.25, 0.5 mg/kg bw from gestation day 17 until day 21 of lactation) dose dependent maternotoxic and foetotoxic effects (prolongation of gestation period and duration of delivery, stillbirths, mortality in new-borns and reduced viability of new-borns of treated dams, gastrointestinal lesions) were observed and may be attributable to the inhibition of prostaglandin synthesis induced by meloxicam. Statistical analysis was performed with two different methods. These analyses showed a significant effect only for prolonged gestational length at the lowest dose (21.94 ± 0.61 days compared to 21.35 ± 0.29 days in the control group) tested. This dose (0.125 mg/kg bw) can be regarded as a LOEL. The NOEL for embryotoxic effects in Sprague Dawley rats was 1 mg/kg bw.

14. Teratogenicity studies have been performed in rats (strains: Sprague Dawley and Chbb:THOM) and rabbits (Chbb:HM) at doses of 1 to 4 mg/kg bw in rats and 1 to 80 mg/kg bw in rabbits. There was no evidence for teratogenic activity in these studies. However, meloxicam showed embryotoxic effects at the lowest doses tested (1 mg/kg) in Chbb:THOM rats and in rabbits. For maternotoxicity, NOELs of 1 and 20 mg/kg bw were identified in Chbb:THOM rats and rabbits, respectively.

15. Meloxicam did not demonstrate genotoxic activity in properly performed gene mutation assays (S*almonella typhimurium* and *Escherichia coli* reversion assays, and HGPRT locus in Chinese hamster lung fibroblasts) or chromosome damage assays (human lymphocytes *in vitro* and micronucleus test in mice *in vivo*). Meloxicam was also negative in a host-mediated gene mutation assay, but this test was not considered reliable for the reason that the positive controls were also without activity. No DNA damage assay has been performed. It is concluded that meloxicam showed no mutagenic potential in the tests performed.

16. No evidence for carcinogenic activity was found in two-year dietary studies in mice and rats with doses of 2, 4 and 8 mg/kg bw daily and 0.4, 0.6 and 0.8 mg/kg bw daily, respectively. This is consistent with the negative findings in the mutagenicity tests.

17. The phototoxic potential of meloxicam was assessed in the human erythrocyte lysis test, rat mast cell degranulation test and in a test of cytotoxicity in murine fibroblasts. Meloxicam showed no phototoxic potential in the first two tests, but was dose-dependently moderately phototoxic in the third assay. In conclusion, meloxicam did not meet the criteria for a phototoxic agent, i.e. positive in two out of three tests.

18. Meloxicam did not show any sensitising potential in Magnusson and Kligman tests using either a parenteral formulation or a gel formulation of meloxicam. Meloxicam also showed no immunogenic activity in mice after an injection in the hind-paw.

19. Studies on the microbiological properties of meloxicam were not submitted and are considered not to be necessary in view of the nature of the compound.

20. Meloxicam is used in human medicine for treatment of rheumatoid arthritis and osteoarthritis. Daily oral doses of 7.5 mg or 15 mg per person are recommended, corresponding to approximately 0.125 or 0.25 mg/kg bw per day. Clinical trial studies including approximately 6000 patients or healthy volunteers have been submitted. However, these studies did not provide sufficient data to enable the establishment of a pharmacological ADI in humans.

21. A pharmacological NOEL could not be derived from the submitted animal or human data. However, based on the data submitted, the rat appears to be the most sensitive species to meloxicam, with Sprague Dawley rats being more sensitive than Wistar rats and Chbb:THOM rats. In the segment III to study in Sprague Dawley rats statistically significant longer length of gestation was recorded in the lowest dose group (21.94 ± 0.61 days compared to 21.35 ± 0.29 days in the control group*)* treated with meloxicam. Although, the difference in the length of gestation is significantly increased in the lowest dose group, it is only a marginal effect. Thus, 0.125 mg/kg bw can be regarded as a LOEL for establishment of an ADI. A safety factor of 100 may be employed as the LOEL is based on dose dependent effects and the effect is considered to be of no biological importance. A toxicological ADI of 1.25 µg/kg bw (equivalent to 75 µg for a 60 kg person) can be established for meloxicam.

22. Residue depletion of ^{14}C-meloxicam in the target species, cattle, was investigated following repeated administration of 0.7 mg/kg bw subcutaneously for 5 days to sixteen Hereford/Friesian calves. The dose regimen used does not correspond to the recommended one i.e. 0.5 mg/kg bw/day.

    Four animals were sacrified at 8 hours, 2, 4 and 8 days after the final dose. The total radioactive residue concentrations 8 hours post last dose were: 8540 µg equivalents/kg in liver, 5070 µg equivalents/kg in kidney, 520 µg equivalents/kg in muscle, 720 µg equivalents/kg in renal fat, 550 µg equivalents/kg in omental fat and 5210 µg equivalents/kg in the injection site. The concentrations declined to reach 1960 µg equivalents/kg in liver, 1480 µg equivalents/kg in kidney, 60 µg equivalents/kg in muscle, 90 µg equivalents/kg in renal fat, 70 µg equivalents/kg in omental fat and 230 µg equivalents/kg in the injection site 4 days after last dose. After 8 days, total residues could only be measured in liver (660 µg equivalents/kg) and kidney (220 µg equivalents/kg).

23. In all edible tissues from cattle, the major single component, in contrast to the profile in urine, was parent meloxicam. The concentrations of unchanged meloxicam were determined by a validated HPLC procedure in muscle and liver and the ratio of parent compound to total residues was determined. At 8 hours and 2 days more than 85% of radioactivity was associated with meloxicam in liver. At 4 days the ratio was approximately 55% and at 8 days approximately 12%. In muscle more than 90% of the radioactivity was parent compound at the three first sacrifice times. At 8 days a ratio of parent compound to total residues could not be established because both the total and the marker residues were below quantifiable levels. The ratio of unchanged meloxicam to total residues in kidney and fat was determined using radio-HPLC and two radio-TLC methods. For kidney the mean overall ratio determined using all radioanalytical results was approximately 40% at 8 hours, 50% at 2 days, 44% at 4 days and 20% at 8 days. For fat this ratio was approximately 60% at 8 hours, thereafter radioactivity was too low for analysis. The concentrations of meloxicam in kidney and fat were not determined by the validated HPLC method, thus the relative distribution of the marker between the target tissues could not be established in precise quantitative terms.

24. From the results of the above presented study the parent substance meloxicam can be determined as the marker residue. 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 that is present in a dressed carcass. In the case of meloxicam an MRL for muscle can be set at approximately twice the limit of quantification of the analytical method.

25. Analytical methods based on HPLC for the determination of meloxicam in muscle, liver and kidney were developed and validated. The validation demonstrates limits of quantification of 10 µg/kg for all target tissues. The limits of detection were 3 µg/kg for liver, 2 µg/kg for muscle and 1.5 µg/kg for kidney.

Conclusions and recommendation

Having considered that:

- an ADI of 1.25 µg/kg bw or 75 µg per person is set for meloxicam,
- parent meloxicam is the marker residue,
- liver, kidney and muscle are the target tissues,
- a ratio of marker residue to total residues of 0.12 and 0.20 can be established, for liver and kidney respectively at 8 days post dose, the nearest time-point when total residues in the standard food package are expected to fall below the ADI,
- the limit of quantification for muscle is 10 µg/kg and nearly all (more than 90%) of the total residues in muscle may be assumed to be unchanged meloxicam at day 8 post dose,
- in fat, the marker residue concentrations could only be measured up to 8 hours after the last treatment, and the contribution of total fat residues to the daily residues was negligible after 8 days (less than 1 µg),
- validated analytical methods are available for monitoring purposes to quantify residues of meloxicam in muscle, liver and kidney;

the Committee recommends the inclusion 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	25 µg/kg 60 µg/kg 35 µg/kg	Muscle Liver Kidney	

Based on these MRLs values, the daily intake will represent about 93% of the ADI.