SCIENTIFIC DISCUSSION

I SUMMARY

Metacam was eligible for the granting of a Community marketing authorisation via the centralised system as it was a product intended for food-producing animals and its active ingredient, meloxicam, had not been authorised for use in food-producing animals on the date of entry into force of Council Regulation (EEC) No 2309/93 (i.e. on 1 January 1995), as provided for under the last indent of Part B of the Annex to that Regulation.

On the 7th of January 1998 the European Commission issued the initial marketing authorisation, valid throughout the European Union, for the veterinary medicinal product Metacam 5 mg/ml solution for injection for cattle. This decision was based on the favourable opinion and the assessment report adopted by the Committee of Veterinary Medicinal Products (CVMP) on 16 July 1997. The marketing authorisation holder is Boehringer Ingelheim Vetmedica, Germany.

Metacam 5 mg/ml solution for injection for dogs and cats and Metacam 1.5 oral suspension for dogs were previously approved in a number of Member States and a number of other countries. As Metacam 5 mg/ml solution for injection for cattle was assessed under the Centralised Procedure, the European Commission deemed it necessary for the companion animal product to be brought under the umbrella of the first authorisation. The companion animal products, currently on the National markets, were withdrawn once the Centralised application was authorised.

The marketing authorisation was subsequently extended to dogs, pigs, cats and horses. The authorisation was renewed in March 2003 and again in December 2007.

Metacam contains meloxicam, a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class belonging to the group of enolic acids. It acts by inhibition of prostaglandin synthesis, thereby exerting anti-inflammatory, analgesic, anti-exudative and antipyretic effects. It reduces leukocyte infiltration into the inflamed tissue. To a minor extent it also inhibits collagen-induced thrombocyte aggregation.

Subcutaneous, intramuscular, intravenous and oral administration are well tolerated; only a slight transient swelling at the injection site following subcutaneous administration was observed in less than 10 % of the cattle treated in clinical studies. Typical adverse drug reactions of NSAIDs such as loss of appetite, vomiting, diarrhoea, faecal occult blood and apathy have occasionally been reported. In dogs, these side effects occur generally within the first treatment week and are in most cases transient and disappear following termination of the treatment but in very rare cases may be serious or fatal.

With regard to Transmissible Spongiform Encephalopathies, the product contains no material of animal origin. The product is therefore out of the scope of the Ph. Eur. monograph and of the "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products".

Based on the original and complementary data presented the Committee for Veterinary Medicinal Products has concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Directive 2001/82/EEC of the European Parliament and of the Council.

II METACAM 5 MG/ML SOLUTION FOR INJECTION FOR CATTLE AND PIGS

QUALITY ASSESSMENT

Metacam solution for injection is a clear yellow solution containing meloxicam (5 mg per ml, 0.5%) as the active ingredient for administration by subcutaneous or intravenous injection in cattle and intramuscular injection in pigs.

The product contains per ml:

Active Ingredient:		Quality standard
Meloxicam	5 mg	B.P

Generic names:	Meloxicam (INN, BAN)
Synonyms:	-
Chemical name:	4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide
Other name:	2H-1,2-benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-1,1-dioxide
CAS no.	-
Laboratory code:	UH-AC 62 XX
Description:	Pastel yellow powder
Molecular formula:	$C_{14}H_{13}N_3O_4S_2$
Molecular weight:	351.4

Evidence of structure was presented in the form of interpreted IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra as well as UV spectra and elemental analysis. Meloxicam is achiral and has no stereoisomers.

Meloxicam is soluble in dimethylformamide, slightly soluble in chloroform and acetone, very slightly soluble in methanol and practically insoluble in water. The pH dependence of the aqueous solubility was shown .The pKa values were 1.09 and 4.14.

There are three known impurities with the current manufacturing method. The impurity profile of three batches produced during 1997 was presented. The specification for total level of related impurities is ≤ 0.3 %. None of the individual impurities were detected. All batches meet the specifications of the pharmacopoeia.

Results of batch analysis were presented. All results are acceptable and within the stated specification limits.

Container:

The containers are colourless glass, Type 1, with rubber stoppers made of ethylene propylene norbornene terpolymer.

Development Pharmaceutics

The active ingredient meloxicam is an achiral drug substance with poor aqueous solubility. The solubility is increased by alkalising agents; Solubilizers were added as in amounts found to prevent precipitation.
Ethanol in a 15% concentration was found to be an effective preservative for the multidose formulation.

The principal manufacturing process has been satisfactorily investigated.

Compatibility of the alkaline solution with the glass vial and closure has been supported by test results in stability studies. The ethylene-propylene-norbornene terpolymer stopper that was chosen offered optimal physical properties and compliance with the requirements of Ph. Eur.

Composition

Active substance: Meloxicam 5 mg BP

Excipient

Ethanol, absolute 150 mg

CONTROL AT INTERMEDIATE STAGES OF THE MANUFACTURING PROCESS

In-process controls include check of pH, filter integrity test, extractable volume, autoclave parameters, particulate contamination and leakage.

CONTROL OF THE FINISHED PRODUCT

The isocratic reversed phase liquid chromatographic method used for simultaneous determination of decomposition and assay has been satisfactorily validated for selectivity, linearity, accuracy and precision. The wavelength was chosen for optimum detection of the decomposition product.

STABILITY

Active Ingredient

In accelerated preformulation studies, meloxicam showed pH-dependent decomposition. Other factors besides pH were not found to influence the stability.

The stability of the drug substance has been investigated in two long-term stability studies, using stability-indicating HPLC methods. Two different packaging materials were investigated. The storage conditions for the studies performed on the bulk packaging material were 25°C/60 %RH, 30°C/70 %RH and 40°C/ambient RH. Test results up to 24 months were reported. No decomposition was observed (LOD 0.2 %). Subsequently stability results up to 60 months have been reported and have been considered satisfactory.

Finished Product

Stability test results were available from two batches with a nominal fill volume of 100 ml. The batches were stored for up to 18 months in upright and horizontal positions respectively. Supplementary stability data from storage up to 24 months of four batches, manufactured in variable scale and filling volume (10 and 50 ml) were included. The first batch was manufactured with a different quality of stopper. Storage conditions were 25°C/60 %RH, 30°C/70 %RH (12 months data) and 40°C/ambient RH (6 months data). Parameters studied included appearance, odour, colour, pH, content of ethanol, content of meloxicam, decomposition and sterility. Standard manufacturing procedures were used and stability data covered the proposed shelf-life of 2 years. The shelf life was subsequently extended to 3 years.

At the request of the CVMP the marketing authorisation holder has forwarded batch analysis data for the first three commercial scale batches to be produced at BASF Labiana S.A. to the EMEA for evaluation as well as the results of the on-going stability programme.

In-use shelf-life

Stability data covered the proposed in-use shelf-life of 1 month. The decomposition rate was not equal for the batches and an increased decomposition rate was also observed after withdrawal of doses. The increase in decomposition estimated or observed during the proposed in-use time of one month was acceptably low. The solution from in-use test samples was later tested and found to have preservative efficacy according to the European Pharmacopoeia. An in-use time of 28 days was proposed for the preserved multi-dose container.

SAFETY ASSESSMENT AND RESIDUES

Safety

The acute oral toxicity for meloxicam was 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 and 98.4 mg/kg for males and females, respectively. For Chbb:THOM rats the oral LD_{50} was 83.5 mg/kg (females and males together). In mini-pigs the oral LD_{50} was approximately 1600 mg/kg, in mice 470 mg/kg and in rabbits 320 mg/kg.

Repeated-dose toxicity was evaluated in 3 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). 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 at 0.2 mg/kg b.w., 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 b.w. derived from a 13 week and a 52 week 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 b.w.) and a NOEL could not be determined.

Reproductive toxicity studies in Sprague Dawley rats covered all stages of the reproduction cycle, segments I-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 resulted in a dose-dependent reduction in implantation rate and increased resorption rate. Fertility indices were unaffected. In the segment II study prolongation of pregnancy and increases in foetal deaths (stillbirths) in the treated groups were observed.

In a segment III study 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 $\pm$ 0.61 days compared to 21.35 $\pm$ 0.29 days in the control group) tested. This dose

(0.125 mg/kg b.w.) can be regarded as a LOEL. The NOEL for embryotoxic effects in Sprague Dawley rats was 1 mg/kg b.w.

Teratogenicity studies have been performed in rats (strains: Sprague Dawley and Chbb:THOM) and Chbb:HM rabbits at doses of 1-4 mg/kg b.w. in rats and 1-80 mg/kg 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 b.w. were identified in Chbb:THOM rats and rabbits, respectively.

Meloxicam did not demonstrate genotoxic activity in properly performed gene mutation assays or Chromosome damage assays. 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.

No evidence for carcinogenic activity was found in two-year dietary studies in mice and rats. This was consistent with the negative findings in the mutagenicity tests.

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. In conclusion, meloxicam did not meet the criteria for a phototoxic agent.

Meloxicam did not show any sensitising potential in Magnusson and Kligman tests. Meloxicam also showed no immunogenic activity in mice.

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

Meloxicam is used in human medicine for treatment of rheumatoid arthritis and osteoarthritis. Clinical trial studies including approximately 6000 patients or healthy volunteers were submitted. However, these studies did not provide sufficient data to enable the establishment of a pharmacological ADI in humans.

A pharmacological NOEL could not be derived from the submitted animal or human data. However, based on the data submitted, the rat appeared to be the most sensitive species to meloxicam. In the segment III-study in rats statistically significant longer length of gestation was recorded in the lowest dose group (21.94 $\pm$ 0.61 days compared to 21.35 $\pm$ 0.29 days in the control group) treated with meloxicam. Although, the difference in the length of gestation was significantly increased in the lowest dose group, it was only a marginal effect. Thus, 0.125 mg/kg b.w. was regarded as a LOEL for the 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 b.w. (equivalent to 75 µg g for a 60 kg person) was established for meloxicam.

Maximum Residue Limits (MRLs)

Meloxicam was 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	
		Equidae	20 µg/kg 65 µg/kg 65 µg/kg	Muscle Liver Kidney	

The excipients used in Metacam 5 mg/ml solution for injection were either included in Annex II of Council Regulation (EEC) No. 2377/90 for all food producing species or do not fall within the scope of Council Regulation (EEC) No. 2377/90 in accordance with the CVMP Position paper on the definition of substances capable of pharmacological action in the context of Council Directive 2001/82/EEC with a particular reference to excipients (EMEA/CVMP/046/00-Rev.2)

Operator Safety

The fact that Metacam injectable solution contains 15% ethanol may give rise to pain at the injection site and hence appropriate wording has been inserted in the Summary of Product Characteristics (SPC).

Furthermore, as there may be individuals sensitive to NSAIDS, it was also considered necessary to amend section 5.12 of the SPC in this respect.

Environmental Safety

The calculations of Predicted Environmental Concentrations in soil using a worst case approach showed that the trigger value for Phase II assessment was not exceeded. Consequently, the clinical use of Metacam will not result in any harmful effects on the environment.

Residues:

Pharmacokinetics

The pharmacokinetic behaviour of meloxicam after a single dose was elucidated in an intravenous pilot study in calves with radiolabelled meloxicam and in a bioavailability study in calves with administration of Metacam 0.5% injectable solution via the IV and SC route in a cross-over design.

The C_{max} of meloxicam from the SC administration was reached after 6 to 8 hours. The absolute availability was variable with values ranging from 44 to 154 % in individual animals. The mean elimination half-life of meloxicam from plasma was approximately 26 hours irrespective of the route of administration. Elimination of total radioactivity from plasma followed the same kinetics as meloxicam with a terminal half-life of approximately 24 hours.

Plasma protein binding ex vivo was found to be > 96.5 % and the same degree of binding was also found in vitro.

At all sacrifice time points investigated in the pilot study the liver contained the highest concentration followed by the kidney and bile. Comparatively low concentrations were found in skeletal muscle and fat.

The proportions of radioactivity excreted in the urine and the faeces were approximately equal (46%) and excretion was completed after 6 days.

Only trace quantities of parent compound were found in the urine. About 5 % of the administered dose was represented by the 5'-hydroxymethylmetabolite and 2 % by the 5'-carboxy metabolite in the urine. The oxalyl metabolite was also detected in cattle. Additionally a polar metabolite (Metabolite 1) was detected and constituted 18% of the administered dose. This metabolite was also detected in bile but not in liver extracts. In some kidney, muscle and fat samples this metabolite was present at concentrations below the LOQ.

The excretion profile in cattle after repeated administration was very similar to that obtained in calves after a single intravenous dose. The elimination kinetics of meloxicam are similar in rats and cattle. The metabolite profile in plasma and excreta was also qualitatively similar in rats, minipigs and cattle (including edible tissues), the only difference being in the routes of excretion. In cattle and minipigs, about 50% of the substance is eliminated in the urine, whereas in the rat approximately 70% was eliminated by this route. The analogies in the pharmacokinetic behaviour of meloxicam in cattle, rats and minipigs indicated that the selected laboratory test species are adequate for an assessment of the toxicological potential of meloxicam and its metabolites present in edible tissues of cattle.

Pharmacokinetic studies were performed in pigs using the recommended doses. The elimination half-life was significantly shorter in pigs than in calves (2.5 h vs 24-26 h). The results of the pharmacokinetic studies and the safety study justify the recommendation of the marketing authorisation holder that treatment can be repeated after 24 hours in pigs depending on the clinical response.

Residue depletion studies

Residue depletion of ^{14}C-meloxicam in the target species, cattle, was investigated following repeated administration of 0.7 mg/kg b.w. subcutaneously for 5 days to Hereford/Friesian calves. The dose regimen used was in excess of the recommended dose i.e. 0.5 mg/kg b.w.

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.

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 the limit of quantification (LOQ) of the analytical method.

Routine analytical method for the detection of residues

A routine analytical method for the determination of meloxicam in liver and muscle was developed based on an HPLC method. The method was not satisfactorily validated regarding limit of detection and specificity towards possible interference from endogenous matrix peaks. Presented validation

results have not been supported by an adequate and complete set of raw data. Therefore, the validity of the claimed limits of quantification, accuracy and precision could not be conclusively assessed.

Withdrawal period

Cattle

The CVMP position paper states that MRLs should henceforth be set for all tissues where residues are detectable. The Committee considered that the absence of adequate residue data in kidney did not allow a statistical calculation to be made from which a withdrawal period could be established to ensure the decline of residues below the MRL for that tissue. However, given the adequacy of data in muscle and liver, that residues in kidney were consistently below those in liver, and that extrapolation of the data from liver tissue points to a withdrawal period of 10 days, the Committee agreed that a withdrawal period of 15 days should be set, the additional 5 days providing an adequate safeguard for the consumer.

For the excipient glycofurol, the Committee considered that at the concentration of the dose in the product to be administered to the target species, it would not be pharmacologically active and that an MRL would not be required.

Pigs

The withdrawal period was based on the MRL values established for pig tissues and two residue depletion studies performed with Metacam 20 mg/ml.

In the first study 8 male and 8 female pigs aged approximately 5 months and weighing 46.5-68.5 kg at dosing were treated with an intramuscular injection of 0.4 mg of a ^{14}C-meloxicam solution corresponding to Metacam 20 mg/ml once daily for 2 days into the neck muscle (the first injection on the right side and the second injection on the left side). The injected amount of meloxicam was 18.6-27.4 mg/animal and treatment and the injected volumes were 0.93-1.37 ml/treatment.

Concentrations of meloxicam in liver, kidney and muscle were above the MRLs established for these tissues (65 µg/kg, 65 µg/kg and 20 µg/kg, respectively) only at 4 hours after the last dose. At 2, 4 and 8 days post last dose the concentrations in those tissues were below the MRLs in all animals and also below the limit of quantification (10 µg/kg).

Concentrations of meloxicam in the muscle of the last injection site were highest at the 4-hour sacrifice with concentrations ranging from 161 to 1509 µg/kg. Two days after the last administration the concentrations of meloxicam were below LOD in all animals. Four days after the last dose the injection site muscle from one animal contained 15.2 µg/kg but the concentrations in the other animals were below LOD. Eight days after the last administration, concentrations of meloxicam in injection site muscle were below LOD in all four animals.

Concentrations of meloxicam in skin/fat from the last injection site ranged between 161 and 354 µg/kg at 4 hours post dose, between 3.2 and 11.3 µg/kg at 2 days and between <LOD and 57.0 at 4 days post last dose. Eight days after the last administration concentrations of meloxicam in skin/fat of the injection site were below LOD in three animals and 4.5 µg/kg in one animal.

Since no meloxicam residues could be detected in liver, kidney or muscle at 2, 4 and 8 days except for the injection site muscle of one animal at 4 days (15.2 µg/kg), a statistical analysis according to the approach recommended by the CVMP (EMEA/CVMP/036/95) was not possible.

The residues in the injection sites were also taken into consideration according to the CVMP position paper (III/5933/94). In this study, the residues in the muscle of the injection site were below the MRL for muscle 2 days after dosing, and remained so at the time-points thereafter. For skin/fat there is no MRL established. The contribution of total residues of meloxicam in skin/fat from the injection sites to the total daily residue intake is small (1 µg at 2 days and 5.3 µg at 4 days, at the most) and at a

withdrawal period of 3 days, the calculated total daily intake will be far below the established ADI for meloxicam (75 µg/person) considering the standard food consumption (0.3 kg muscle, 0.1 kg liver, 0.05 kg skin/fat and 0.05 kg kidney). From this study a withdrawal period of 3 days seemed acceptable.

In the second study twelve lactating sows of 1-4 years of age (body weight range 183-281 kg) and their litters were assigned to one of three test groups and each sow received two consecutive intramuscular injections of Metacam 20 mg/ml at a dose of 0.4 mg/kg body weight. The first injection was given on Day 1, the second on Day 2. The injected amount of meloxicam was 73.2-112.4 mg/animal and treatment and the injected volumes were 3.66-5.62 ml/treatment.

Group I was sacrificed at Day 4 (i.e. 2 and 3 days after injection), group II was sacrificed at Day 6 (i.e. 4 and 5 days after injection) and group III was sacrificed at Day 7 (i.e. 5 and 6 days after injection). Tissue samples from group I included liver, kidneys, skeletal muscle and injection sites. For group II and III only injection sites were collected.

At Days 2 and 3 after injection no quantifiable residue concentrations were found in kidney, liver and 3 out of 4 muscle samples. One muscle sample showed a residue concentration of approximately 11.6 µg/kg (2 days after injection). Meloxicam was above the limit of quantification (LOQ, 10 µg/kg) in injection site samples of 3 out of 4 sows. One left injection site sample showed a residue concentration of 76.5 µg/kg at 3 days after injection whereas 3 samples of the right injection site (i.e. 2 days after injection) presented residue concentrations in the range of 18.4-164.7 µg/kg.

For sows slaughtered on Day 6 (4 and 5 days after injection), one injection site sample (4 days after injection) presented a residue concentration of approximately 14.6 µg/kg of meloxicam (i.e. below the MRL of 20 µg/kg). In the injection sites of the three remaining sows, meloxicam levels were below the LOQ.
There were no meloxicam residues above the LOQ in injection site samples from animals slaughtered at day 7 (5 and 6 days after injection).

The results showed that all residues of meloxicam in liver, kidney, skeletal muscle and injection sites were below their MRL values 4 days after the second injection. Given the data from the second residue depletion study, a withdrawal period of 5 days was established for meat and offal from pigs treated with Metacam 20 mg/ml solution for injection.

A study intended to show bioequivalence of Metacam 5 mg/ml and Metacam 20 mg/ml was submitted. Bioequivalence could not be statistically demonstrated between the two formulations of Metacam following intramuscular administration to pigs. However, both Cmax and AUC was higher for Metacam 20 mg/ml than for Metacam 5 mg/ml. Consequently, the residue studies performed with Metacam 20 mg/ml solution can be used for establishing a withdrawal period for Metacam 5 mg/ml solution. Regarding injection site residues, the higher injection site volumes injected to the sows weighing 183-281 kg resulted in higher amount of residues in the injection site compared to the first study in smaller pigs weighing 46.5-68.5 kg. Metacam 5 mg/ml is intended for smaller pigs only with injected amounts of meloxicam of approximately 15-30 mg/treatment and injection volumes of 3-6 ml, so the results from the residue depletion study performed with Metacam 20 mg/ml in sows can be considered as a worst-case scenario concerning safety of the consumer.

A withdrawal period of 5 days for meat and offal from pigs treated with Metacam 5 mg/ml solution for injection as proposed by the marketing authorisation holder was considered acceptable.

Routine Analytical Methods

A routine analytical method based on HPLC for determination of meloxicam in bovine tissues was presented in the ISO 78/2 format and validated for milk, muscle, liver and kidney according to Volume VI of the Rules Governing Medicinal Products in the European Community. The limits of quantification are 2.5 µg/kg for milk and 10 µg/kg for muscle, liver and kidney. The limits of detection are 1.5 µg/kg for milk, 2 µg/kg for muscle, 3 µg/kg for liver and 1.5 µg/kg for kidney.

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 is 10 µg/kg for all porcine edible tissues and the limits of detection are 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.

The residue depletion studies were conducted according to the current guidelines and the withdrawal periods proposed by the marketing authorisation holder were accepted.

EFFICACY ASSESSMENT

Pharmacodynamics:

Meloxicam inhibits the synthesis of prostaglandin PGE2 by inhibiting the constitutive cyclo-oxygenase and the inducible cyclo-oxygenase. Compared to several other NSAID´s tested meloxicam was shown to be the most selective inhibitor of inducible cyclo-oxygenase activity.

Primary pharmacological effects include anti-inflammatory, anti-pyretic and analgesic properties in several species including humans, probably due to inhibition of inducible cyclo-oxygenase. 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 effect on the cardiovascular and respiratory systems in anaesthetised 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.

With regard to 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.

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 cyclo-oxygenase inhibition.

Tolerance in the target species:

Mild erosions in the abomasal mucosa were observed in single animals in the experimental studies. No adverse reactions were seen in a tolerance study up to three times the recommended dose during 5 days with intravenous administration except for thickening over the jugular vein at the injection site. Metacam was well tolerated in the field trials and no adverse reactions were reported. The vast majority of the animals in these studies received subcutaneous injections, which were not associated with any marked local toxicity. Safety was not documented in the pregnant or lactating animal and therefore is suitably contra-indicated.

The tolerance of Metacam 20 mg/ml was tested in 5-6 months old pigs weighing from 49 to 60 kg. Twenty-four animals were randomly allocated to four groups. The groups were treated with 0, 0.4, 1.2 and 2.0 mg/kg intramuscularly once daily for 6 consecutive days.

The animals were observed daily for signs of toxicity. Body weight, food and water consumption, heart rate, respiratory rate and rectal temperature were recorded. No signs of illness occurred and all studied parameters were similar in all groups. Autopsy revealed no changes that could be related to treatment. However, moderate inflammatory reactions were found at the injection sites of the animals treated with the highest doses. The reactions after the recommended dose, 0.4 mg/kg b.w. were similar to those after injection of physiological saline.

An established endotoxin model was used in an earlier submitted dose finding study. The results showed that Metacam has a wide therapeutic window in pigs. The statistical calculation showed that 0.4 mg/kg b.w. was the optimal dose. The tissue irritating effect of Metacam in laboratory animals, dogs ,cats and cattle was reported in earlier submitted studies. The Metacam formulations were found to be well tolerated. The results from the pig studies show similar results. No general or local reactions were observed after treatment with the recommended dose for 6 consecutive days.

Clinical studies (cattle)

Meloxicam was demonstrated to have anti-inflammatory, anti-exudative and analgesic activity.

The antipyretic effect of Metacam 0.5% was tested in single dose titration studies in calves with experimentally induced or naturally transmitted respiratory infection. In two studies oxytetracycline (5 mg/kg) was given 12 hours after dosing of Metacam. A significant decrease in temperature was noted after 12 hours compared to placebo from 0.3 mg/kg and above and the optimal dose was found to be in the range of 0.5 - 0.7 mg/kg. The duration of the observation period (12h) was too short to demonstrate antipyretic effect up to 24 hours in these studies. Meloxicam (0.5 mg/kg) reduced clinical signs significantly and abolished the increase in blood thromboxane B_2 seen in the control group after endotoxin administration. In one study involving a respiratory infection model in calves, combination treatment with Metacam 0.5 mg/kg and oxytetracycline 10 mg/kg was significantly more effective in reducing fever and clinical signs of infection than oxytetracycline monotherapy.

The field trials performed in calves with acute respiratory infections were well conducted and reported. Approximately 500 animals were included, the majority receiving a single injection of Metacam in combination with antibiotics and compared to placebo treatment. In the pivotal controlled trial, randomisation was performed on pairs of animals with similar severity of disease. A total of 326 pairs were available for evaluation. Addition of a single subcutaneous administration of Metacam to antibacterial therapy significantly improved clinical parameters and reduced fever compared to antibiotics alone.

The indication proposed is for use in acute respiratory infection in combination with appropriate antibiotic therapy to reduce clinical symptoms in calves and young cattle, by single subcutaneous or intravenous injection at a dosage of 0.5mg/kg bodyweight.

Laboratory trials (Pigs)

<u>Bioequivalence and Bioavailability of Metacam 5 mg/ml and 20 mg/ml Solutions for Injection in Pigs</u>
Twelve castrated healthy pigs weighing from 40 to 48.5 kg were used in the study which was of 2x2 cross-over design. The wash-out period between the treatments was 7 days. The test solutions were injected intramuscularly into the thigh to ensure proper intramuscular injection. Seven days after the last i.m. injection the solutions were administered intravenously to allow calculation of bioavailability.

The dose used was 0.4 mg/kg b.w. Blood was collected for analysis of the plasma concentration of meloxicam at 10, 20, 30, 45, 60, 90, 120 and 150 min and at 3, 4, 6, 8, 12, 24, 36 and 48 hours after treatment. Meloxicam in plasma was analysed by a fully validated HPLC method. No general or local reactions which could be attributed to the test solutions could be observed.

The major pharmacokinetic parameters are tabulated below (means):

Parameter	Metacam 5 mg/ml		Metacam 20 mg/ml	
	i.m.	i.,v,.	i.m.	i.v.
t_{max} hours	0.90	0.17	0.60	0.19
C_{max} ng/ml	1086.08	1831.67	1455.00	1876.67
AUC ngh/ml	4860.79	5180.53	5439.11	4690.97
$t_{1/2}$ hours	2.46	2.48	2.67	2.56
Cl (i.m.) or Cl (i.v.) ml/min-kg	1.56	1.51	1.34	1.51
V (i.m.) or V (i.v.) l/kg	0.31	0.31	0.30	0.34

The calculated bioavailability of Metacam 5 mg/ml was 0.87 and of Metacam 20 mg/ml 1.08 with 95% confidence intervals of 0.63 – 1.20 and 0.79 – 1,42, respectively.

The plasma concentration curves were superimposed from 2.5 h and onwards, but statistical bioequivalence of Metacam 5 mg/ml and Metacam 20 mg/ml could not be shown in accordance with the current guideline. The antilog of the 90% confidence intervals for the difference between the two Metacam formulations for Cmax and AUC did not fall within the limits of the equivalence range of 0.800 – 1.250. The actual ranges were 0.741 – 1.036 for the AUC and 0.617 – 0.881 for Cmax.

However, it is argued in the supplementary expert report that the criteria for bioequivalence as laid out in the guideline EMEA/CVMP/016/00-FINAL can be considered as being fulfilled. According to the guideline, the lower limit of the 90% confidence interval for the ratio of the two AUC means might be below 80% in case of a large efficacy window and this is the case for Metacam. The expert refers to the earlier submitted pivotal dose titration study where the 5 mg/ml solution for injection of Metacam was used. Three different doses 0.2, 0.4 and 0.8 mg/kg b.w. were tested in an endotoxin model in pigs. The total clinical score was significantly reduced by all doses and there were no significant differences between the highest dose groups. An effective dose of 0.43 mg/kg was calculated using a linear spline model. On request from the CVMP the marketing authorisation holder submitted detailed information on the statistical model and how it was applied in the study.

Field trials (pigs)

Efficacy of Metacam 20 mg/ml was demonstrated in a placebo controlled study where pigs suffering from non-infectious locomotor disorders were included. The study was earlier assessed and only a very short summary is given here.

The dominating category of animals in both groups was pregnant and non-pregnant sows and gilts, but also fattening pigs were included. One hundred and three animals in the Metacam group could be evaluated on day 4 after treatment and 106 in the placebo group. The primary parameter was the clinical lameness score. The score was significantly lower in the Metacam group No clinical symptoms were recorded in 49% of the animals of the Metacam group on day 4, the corresponding figure for the placebo group was 27%.

Conclusion on the Clinical Part (Pigs)

A study demonstrating clinical efficacy of Metacam 20 mg/ml for the treatment of pigs suffering from non-infectious locomotor disorders was earlier submitted and assessed.

Metacam 20 mg/ml was also found to be as effective as another NSAID, authorised by the national procedure in a number of member states, used in combination with antibiotics for the treatment of the MMA syndrome in sows.

The Committee noted the lack of demonstrated statistical bioequivalence between Metacam 20 mg/ml and Metacam 5 mg/ml. However, given the wide therapeutic range of the product, the Committee considered that equivalence of therapeutic effect had been shown.

RISK-BENEFIT ASSESSMENT AND CONCLUSION

The Committee for Veterinary Medicinal Products agreed to set the withdrawal period for meat and offal at 15 days.
An Acceptable Daily Intake (ADI) of 1.25 µg/kg b.w. (i.e. 75 µg/person) was established by the CVMP by applying a safety factor of 100 to the Lowest Observed Effect Level (LOEL) of 0.125 mg/kg for effects on the gestation length in a reproductive toxicity study in Sprague Dawley rats. The following MRLs were established for bovine tissues: muscle 20 µg/kg, liver 65 µg/kg; kidney 65 µg/kg, milk 15 µg/kg and for porcine tissues: muscle 20 µg/kg, liver and kidney 65 µg/kg.
The residue depletion studies were performed according to the current guidelines and the following withdrawal periods were established: cattle, meat and offal 15 days, pigs: meat and offal 5 days.
There appears to be no risk for the person administering the drug. Meloxicam is authorised for symptomatic treatment of rheumatoid arthritis in humans and is lack of skin and eye irritating effects.
No general reactions were observed in the target species after treatment with the recommended doses. However, swellings at the injection sites can occur after subcutaneous and intramuscular administration.
The effective clinical dose was determined in a study using a classical endotoxin model. The dose was calculated to be 0.4 mg/kg b.w.
The claimed indication was sufficiently supported by the results of the clinical study.

III METACAM 20 MG/ML SOLUTION FOR INJECTION FOR CATTLE , PIGS AND HORSES

Composition

Ingredient	Amount [mg/ml]	Function
Meloxicam B.P.	20.00	Active ingredient
Ethanol anhydrous* (Ph.Eur. 3)	150.00	Preservative

* Ethanol 96% may be used instead of ethanol 99.5% (it must correspond to the Ph. Eur monograph)

Container

Colourless glass injection vials of 50 ml and 100 ml sealed with a rubber stopper made of ethylene-propylene- norborene- terpolymer. Both packaging materials conform to the European Pharmacopoeia Monograph (Ph. Eur).

Clinical trial formulations

Three different formulations were used in the clinical trials. Formulation A was the formulation applied for. Formulation B is Metacam 5 mg/ml solution for injection for cattle already on the market. Formulation C (10 mg/ml) is a single dose preparation containing no ethanol and presented in 10 ml ampoules.

Development Pharmaceutics

The aim of the development work was to obtain an injection for cattle with a higher concentration of drug substance than the earlier approved Metacam 5 mg/ml solution for injection for cattle. The work was based on previous experience with the 5 mg/ml solution for injection. The active ingredient meloxicam is an achiral drug substance with poor aqueous solubility. The solubility has been increased by the addition of alkalising agents.

A suitable preservative for a multi-dose formulation was sought. Ethanol at a concentration of 15% was found to be effective. This concentration was effective in fulfilling criterion A of the Ph. Eur. test "Efficacy of Antimicrobial Preservation".

Compatibility of the alkaline solution and the glass vial was supported by the results of stability studies.

METHOD OF MANUFACTURE

The typical batch-size may vary from 100 kg to 1041.4 kg (equivalent to 1025 litres). The manufacturing formula for a 1025 litre batch was presented.

The manufacturing process was also described. The successive addition of ingredients, stirring, heating and cooling were shown in a flowchart over the manufacturing process in the manufacturers documentation and described in the tabulated Expert Report. Standard manufacturing procedures were used.

The bottles are filled under nitrogen as a routine procedure, which corresponds to current technical standards. The product is sterilised in the container at 121°C for a minimum of 15 minutes. In-process controls include check of appearance, pH, relative density, filter integrity test, filling mass, completeness of solution (clear solution, free of particles).

The product is manufactured using a standard process, which employs conventional techniques only. The critical process parameters have been validated.

CONTROL OF STARTING MATERIALS

Active substance

The active substance is the same as previously approved for Metacam 5 mg/ml solution for injection for cattle and pigs. The specifications and routine tests were presented. Batches manufactured for clinical study and three normal production batches manufactured have been presented. Solvents used in earlier steps of the synthesis were also tested on the production batches. The results show that the purification method effectively removes these solvents. The results were satisfactory, being within the specification limits.

Other ingredients

For the other ingredients appropriate monographs have been provided.

Excipients listed in a pharmacopoeia

Each batch of excipient is analysed in accordance with respective pharmacopoeia.

Excipients not listed in a pharmacopoeia

Other excipients are tested according to the manufacturers own specifications and are equivalent to the methods in the European Pharmacopoeia.

CONTROL TESTS OF THE FINISHED PRODUCT
Specification and routine testing

The quality of the finished product at release and throughout its shelf life is assured by the proposed analytical procedures and limits. These include tests for appearance, colour, clarity, extractable volume, identity, assay, pH and sterility.

Validation

The validation of the analytical methods was presented. The reverse phase liquid chromatographic method used for identification and for simultaneous determination of decomposition and content of meloxicam has been satisfactorily validated for selectivity, linearity, accuracy, precision and robustness. The GC method used for identification and for determination of the content of ethanol has been satisfactorily validated for selectivity, linearity, accuracy, precision and robustness.

The LC method used for identification and for determination of the content of disodium edetate has been satisfactorily validated for selectivity, linearity, accuracy, precision and robustness.

Batch analysis

The results of batch analysis were presented. All results were within the stated specifications.

STABILITY
Stability Tests on the Active substance

The stability tests on active substance were presented. Two stability studies are presented. Both studies are the same as have been presented earlier for Metacam 5 mg/ml solution for injection for cattle with the addition of complementary data for the second study that was ongoing at that time. The marketing authorisation holder has also provided additional data. The proposed re-test period of 60 months was considered acceptable.

Stability tests on the finished product

Stability studies have been started with three production scale batches. The marketing authorisation holder has chosen the 50 ml pack size based on the theory that that the smallest container is the most critical. Results from the batches stored for up to 6 months at 4°C, 25°C 60%RH, 30°C 75%RH and 40°C 75%RH have been submitted. The batches have been tested according to the shelf-life specifications.

The presented results show no or no relevant changes neither in the organoleptic, physico-chemical or chemical properties nor in the packaging material. A further stability report from storage of samples for up to 24 months was also submitted. Subsequently, the shelf life has been extended to 3 years.

In-use Stability

Two batches were tested after being stored at 25°C 60%RH for 7 weeks. Three doses of 4 ml were taken from each vial at day 1. Four doses of 4 ml were taken from each vial at day 7. Storage was continued up 28 days. The samples were tested initially and after 28 days. The test for efficacy of antimicrobial preservation according to Ph. Eur. was performed initially and after 28 days. No changes were observed.

Preservative efficacy test

The concentration of ethanol is the same as used in Metacam 5 mg/ml. An experimental batch was manufactured with an ethanol content of 90%. This batch was stored for 21 months under monitored conditions 21°C± 2°C and was used for a preservative efficacy test. The initial value for the ethanol content at the beginning of the study was 87.3%. The tested samples complied with the limits of level A of the preservative efficacy test of the Ph. Eur. This finding was supported by the results of the current APE test after storage over a period of 24 months at 25°C/60% RH.

Light exposure was also investigated. Irradiation was for 18 hours, at 1.2 million lux hours (Xenon lamp). The vials were placed up- right unlabelled, upright wrapped in aluminium foil, horizontal labelled and horizontal unlabelled. The samples were stored at 25°C 60%RH for 4 weeks before the study. The results indicate that light exposure does not affect the quality of the product.

Clarification was, however, sought on the effect on the integrity of the container of an increased number of doses withdrawn with the extension of the use of the product to pigs. A study demonstrating the integrity of closures (fragmentation and self-sealability) according to the specifications in the European Pharmacopeia was submitted. The requirement of the European Pharmacopeia was met also after the highest calculated number of doses withdrawn for use in pigs.

SAFETY
Pharmacokinetics

The pharmacokinetics after intravenous injection was earlier documented in calves using ^{14}C-labelled meloxicam. The elimination half-life was found to be 24-26 hours. The protein binding was >95% over a wide range of concentrations. The results from repeated dose studies showed that meloxicam accumulates in plasma after repeated daily administration. The bioavailability of meloxicam after subcutaneous injection of the recommended dose (0.5 mg/kg) of the 0.5% solution was 92% when compared with intravenous (i.v.) injection. The studies performed were previously assessed in the original dossier for Metacam solution for injection 5 mg/ml for cattle.

A new study demonstrating bioequivalence in cattle between Metacam 5 mg/ml and Metacam 20 mg/ml was submitted.

All pharmacokinetic studies submitted in the residue documentation for Metacam 20 mg/ml solution for injection were included in the original application for the establishment of bovine Maximum

Residue Limits (MRLs) for meloxicam or with subsequent applications for their modification and extension to include the target tissue matrix bovine milk.

The pharmacokinetics and metabolism of meloxicam have been extensively studied in the mouse, rat, dog, minipig, baboon, human and the target species cattle and have been fully reported and evaluated by the CVMP.

Toxicological Studies

Toxicological studies were submitted previously. From a consumer safety point of view, it is important to compare metabolism in the laboratory species used in the toxicology studies with metabolism in the target species. The metabolite profile in plasma and excreta is qualitatively similar in rats, minipigs and cattle (including edible tissues), the only difference lying in the routes of excretion. In cattle and minipigs, about 50% of the substance is eliminated in the urine, whereas in the rat about 70% is eliminated by this route. The major metabolites found in the three species were the 5'-hydroxymethyl-and 5'-carboxy-metabolites. The oxalyl metabolite was found in rats, humans and cattle, but not in minipigs and mice. A highly polar metabolite was found in cattle urine, but not in urine from the other species. In all edible tissues and milk, the major component, in contrast to the profile in urine, was parent meloxicam. Low levels of the 5'-hydroxy-, 5'-carboxy- and oxalyl metabolites were also present in edible tissues and milk. The unidentified polar metabolite was not detected in liver, with trace amounts detected in the other edible tissues of cattle.

Given the analogies in the pharmacokinetic behaviour of meloxicam in cattle, rats and minipigs, the selected laboratory species have adequately assessed the toxicological potential of the metabolites of meloxicam found in the edible tissues (including milk) of cattle.

In laboratory species, the NOEL for teratogenicity/fetotoxicity is 1 mg/kg in Sprague Drawley rats and below 1 mg/kg in Chbb:Thom rats and in rabbits.

More than 800 calves were included in the clinical studies. There were no age limitations for inclusion, consequently the studies included also calves younger than 3 weeks. Efficacy was proven and no serious adverse reactions occurred. Metacam is centrally authorised and according to the latest PSUR, the incidence of SADRs was 0.0005%.

The study of tolerance in pigs demonstrated an adverse effect on the gastric mucosa at the recommended dose. However, microscopic evidence of gastric bleeding was found in one out of six animals and the treatment period was three times longer than the recommended. No signs of gastric bleeding occurred in pigs treated with 5X the recommended dose for the same time period nor in the field studies which included more than 200 pigs. A warning in the SPC point 5.4 was therefore not considered necessary.
An ADI of 1.25 µg/kg b.w. (i.e. 75µg/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 for effects on gestational length in a reproductive toxicity study in Sprague Dawley rats.

The residue depletion study was performed according to the requirements of the Rules Governing Veterinary Medicinal Products in the European Union, Volume 6. The study was included in the application submitted for the extension of MRLs for meloxicam to include the target species swine.

The withdrawal period of 5 days proposed by the marketing authorisation holder is acceptable.

With regard to ecotoxicity, the marketing authorisation holder has demonstrated that the assessment is complete at Phase 1.

USER SAFETY

The tolerability of the formulation of meloxicam for human use was good after intravenous and subcutaneous administration to man. Intravenous doses up to 60 mg in healthy volunteers did not cause side effects. A parenteral administration in humans has been performed in various studies with up to 60 mg meloxicam per person. The only ingredient liable to cause injury is ethanol. The other components, including meloxicam, have been shown to be safe in humans. The ethanol content has been calculated to be 1.13 g in the whole dose of 5 ml Metacam 20 mg/ml recommended for a 250 kg sow. This amount of ethanol can lead to a mild transient local pain in sensitive individuals.

It is however concluded that no special precautions are needed for the use of Metacam 20 mg/ml solution for injection for cattle and pigs except for those individuals known to be sensitive to NSAIDs and who should avoid contact with the product.

Submitted studies showed that meloxicam is neither a dermal nor an eye irritant. The person administering the solution is therefore not exposed to any risk. No special precautions were deemed necessary. Metacam 20 mg/ml solution for injection appears to be safe when used as proposed and does not pose any risk for the person administering the product. The SPC text "Individuals sensitive to NSAIDs should avoid contact" was considered sufficient.

ECOTOXICITY

An Environmental Risk Assessment was provided for the product. The PECS were calculated for calves/young calves, piglets, fattening pigs and adult pigs at two different depths of ploughing (5 and 25 cm).

Subpopulation	PEC in µg/kg soil	
	25 cm ploughing	5 cm ploughing
Calves/young calves	1.31	6.07
Piglets	1.29	6.18
Fattening pigs	0.89	4.31
Adult pigs	0.27	1.33

All PECs are below the trigger for further phase II evaluation (EMEA: 10 and VICH: 100) on the basis of nitrogen as the limiting factor. On the basis of calculations using both nitrogen and phosphorus as limiting factors for manure spreading, the PEC trigger value of the current VICH phase I guideline (EMEA/CVMP/VICH/592/98-FINAL) was not exceeded for the product.

Residue Documentation

Cattle

Sixteen cattle were given a single subcutaneous injection of 0.5 mg ^{14}C-meloxicam/kg b.w. (0.5% solution of Metacam). The specific activity and radiochemical purity of the labelled substance were 20.53 µCi/mg and > 99% respectively Groups of 4 cattle were sacrificed at 2, 4, 6 and 8 days after administration and the concentrations of radioactivity and meloxicam were determined in muscle, injection site muscle, liver and kidney. Fat was not analysed in this study due to the previous decision of the CVMP not to establish an MRL for fat. Radioactivity was measured by Liquid Scintillation Counting (LSC) and the concentrations of meloxicam in tissues were determined by a validated HPLC procedure. The limits of detection of the method were 3.0, 2.0 and 1.5 µg/kg for liver, muscle and kidney, respectively. The limit of quantification was 10 µg/kg for all target tissues.

The individual and mean concentrations of radioactivity in the tissues at different time-points were presented. The individual and mean concentrations of meloxicam in the tissues at different time-points were also shown. This residue depletion study was performed according to the requirements of the Rules Governing Medicinal Products in the European Community, Volume VI. The study was

included in the application submitted for the modification of MRLs for meloxicam and was evaluated by the CVMP.

Eight lactating dairy cows were administered a single subcutaneous injection of 0.5 mg ^{14}C-meloxicam/kg b.w. (2.0% solution of Metacam). Milk was collected twice daily, once in the morning and once in the afternoon, after an interval of approximately 6 hours, for 10 days. Blood samples were taken from the jugular vein at different time-points up to 10 days post dose for the determination of pharmacokinetic parameters.

Radioactivity was measured by LSC and the concentrations of meloxicam in milk and plasma were determined by a validated HPLC procedure. The limit of detection was 1.5 ng/ml for milk and 3 ng/ml for plasma and the limit of quantification was 2.5 ng/ml for milk and 10 ng/ml for plasma for the HPLC method. Subsamples were taken from representative milk samples on days 1 and 2 for metabolite profiling by HPLC and TLC.

Mean peak plasma radioactivity concentrations of 3291 ng equivalents/ml (low milk yield cows) and 2536 ng equivalents/ml (high milk yield cows) occurred at 2-3 hours and mean peak plasma meloxicam concentrations of 2875 ng/ml (low milk yield cows) and 2495 ng/ml (high milk yield cows) occurred at 4 hours. Half-lives for decline in plasma radioactivity and meloxicam were 23-27 hours and 17.5 hours, respectively. The area under the mean plasma meloxicam concentration versus time (AUC_∞) was 86.3 $\mu g.hml^{-1}$ for the low milk yield cows and 76.4 $\mu g.hml^{-1}$ for the high milk yield cows.

Mean concentrations of radioactivity in the afternoon milk samples declined with half-lives of 20.8 and 21.4 hours in the high and low yield animals, respectively. 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.

The metabolism of meloxicam was similar in low and high milk yield cows. Meloxicam was the major radioactive component resolved and accounted for approximately 80% of the radioactivity. Two other components were also detected. The mean concentrations of radioactivity and the mean and individual concentrations of meloxicam in milk and the ratio of meloxicam to total residues were provided.

This residue depletion study was performed according to the requirements of the Rules Governing Medicinal Products in the European community, Volume VI. The study was included in the application submitted for the extension of MRLs for meloxicam to include the matrix milk and was evaluated by the CVMP.

Pigs

<u>^{14}C-Meloxicam: Metabolism and residues in tissues following intramuscular administration to pigs.</u>

Pigs (8 male and 8 female of Large White Hybrids; aged approx. 5 months; bodyweight 46.5-68.5 kg at dosing) were administered an intramuscular injection of 0.4 mg ^{14}C-meloxicam/kg b.w. once daily for 2 days into the neck muscle (the first injection on right side and the second on the left side). Meloxicam was labelled in the carboxamide moiety and the ^{14}C-meloxicam (specific activity 0.76 MBq/mg) was diluted with unlabelled meloxicam to specific activities of 206-380 kBq/mg and formulated in a solution corresponding to Metacam® 20 mg/ml solution for injection, the proprietary product proposed for use in pigs.

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 liquid scintillation counting and concentrations of meloxicam were determined by a validated HPLC procedure.

Groups of four animals (2 male and 2 female) were sacrificed at 4 hours and at 2, 4 and 8 days after the final dose. Liver, kidneys, skeletal muscle, fat (renal and omental) and muscle and skin/fat from the two injection sites were taken and measured for radioactivity by LSC. The concentrations of meloxicam in the tissue samples were determined using a validated HPLC method with LC/MS detection.

Results: The actual doses administered to each pig were in the range 0.36 – 0.44 mg/kg bodyweight. The mean total recovery of radioactivity was 85.9 % of the total dose. Amounts of radioactivity excreted in faeces (mean of 45.2 %) were slightly higher than the amounts excreted in urine (mean of 38.6 %).

Plasma radioactivity concentrations increased to a maximum mean concentration of 1662 ng equivalents/ml at one 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 major faecal metabolite excreted during 5 days was the 5-carboxy metabolite (UH-AC11), which accounted for approximately 65 % of the faecal radioactivity. Meloxicam accounted for 2.8 % of the faecal radioactivity. The metabolite profiles obtained in selected samples of urine by HPLC and TLC revealed that unchanged meloxicam was only a minor component and accounted for a maximum of 2.5 % of the urinary radioactivity in the samples measured. The major urinary metabolites were identified by co-chromatography as 5-carboxy (UH-AC110) and 5-hydroxymethyl (AF-UH1SE) metabolites and accounted for 19.8-33.3 % and 31.0-43.4 % respectively of metabolites in urine collected during the 24 hours after the 2nd dose. A polar metabolite (Met 1) accounted for 12.0-15.6 % but was not identified. Possible identity was the reference substance BIB08032Na (N-(2-[thiazolylcarboxylic acid]) oxamic acid or the known metabolite DS-AC2Na (oxalyl-metabolite). Four other unknown metabolites were separated by HPLC and represented < 10 % of the urinary radioactivity.

Samples of tissues from animals sacrificed at 4 hours were extracted with organic solvent and the concentrated extracts were analysed by HPLC and TLC. Liver samples at 4 hours, 2 days and 4 days and kidneys at 2 and 4 days were treated with protease enzyme prior to extraction. Mean recoveries of radioactivity in the extracts for the 4-hour samples were in the range 68-92 % except for skin/fat where mean recovery was 27 %. In the 2-and 4-day liver and kidney samples, mean recoveries of radioactivity in the extracts were 52.8-77.3 %. The major component resolved in all tissue extracts from the 4-hour sacrifice corresponded to unchanged meloxicam except for liver where it was the polar metabolite (Met 1). The mean proportions of radioactive components in the tissue extracts are shown in table 1:

Table 1. Proportions of radioactive components in tissue extracts from pigs

Component	Liver			Kidneys		Muscle	Fat	Skin/ fat	Injection site*	
	4-hour	2-day	4-day	4-hour	2-day	4-hour	4-hour	4-hour	Muscle	Skin/fat
Meloxicam	17.2	nd	nd	36.2	nd	47.6	42.7	6.6	52.4	11.4
AF-UH1SE	3.1	4.5	2.0	7.9	5.4	6.0	8.9	2.7	5.4	2.2
UH-AC110	2.5	7.9	13.2	6.8	5.0	1.2	3.2	0.9	1.9	0.9
Polars	37.1	15.8	17.1	16.7	13.8	2.2	14.1	9.0	5.3	14.3
Unextracted	31.9	32.5	22.7	17.6	47.3	22.1	8.0	72.9	11.4	64.5

* injection site 2 taken at the 4-hour sacrifice
nd = not detected

The proposed metabolic pathway of meloxicam in pigs after intramuscular administration is oxidation of the methyl group of the thiazole ring to give AF-UH1SE and UH-AC110. Oxidative cleavage of the double bond in the benzothiazine part of meloxicam and UH-AC110 gives DS-AC2Na and BIB08032Na respectively.

Concentrations of radioactivity in edible tissues were highest in liver and kidney at each sacrifice time. Levels of radioactivity in muscle were very low and were essentially only detected at the first sacrifice time. Levels of radioactivity in fat and skin/fat were only detected at the 4-hour sacrifice time.

Concentrations of meloxicam in edible tissues above the limit of quantification were only detected at the 4-hour sacrifice except in a few samples of injection sites. Ratios of meloxicam to total radioactive residues could only be calculated for the 4-hour sacrifice. Mean and individual total concentrations of radioactivity, mean and individual meloxicam concentrations and mean ratios of meloxicam to total radioactive residues in pig tissues at various time-points are shown in table 2.

Table 2 Concentrations of radioactivity and meloxicam in edible tissues at various times after two consecutive daily intramuscular doses of ^{14}C-meloxicam at a nominal dose of 0.4 mg/kg bodyweight/day

	Sacrifice time	**TRR mean and individual data (µg equivalents/kg)**	**Meloxicam concentration mean and individual data (µg/kg)**	**Mean ratio meloxicam to TRR**
Liver	4 hours	999 (923,1043, 1000, 1029)	446 (325, 615, 399, 446)	0.44
	2 days	175 (174, 208, 170, 148)	<LOD	-
	4 days	91.1 (95.6, 74.5, 96.8, 97.4)	<LOD	-
	8 days	44.8 (48.3, 52.1, 39.7, 37.8)	<LOD	-
Kidney	4 hours	1450(1074,1764,1657,1304)	845 (269, 993, 1313, 804)	0.56
	2 days	105 (151, 99.5, 76.4, 94.9)	2.5[#]	-
	4 days	63.6 (57.6, 57.4, 81.3, 58.2)	<LOD	-
	8 days	20.5 (22.4, 13.9, 25.8, 19.9)	<LOD	-
Muscle	4 hours	55.6 (47.6, 72.1, 51.0, 51.6)	37.6 (32.6, 49.1, 36.4, 2.2)	0.67
	2 days	7.6* (nd, 6.9, nd, 8.3)	<LOD	-
	4 days	nd	<LOD	-
	8 days	nd	<LOD	-
Fat	4 hours	189 (93.1, 196, 318, 148)	77.7 (17.5, 77.8, 96.4, 119)	0.42
	2 days	nd	4.5[# ¤]	-
	4 days	nd	<LOD	-
	8 days	nd	<LOD	-
Skin/fat	4 hours	118 (120, 133, 103, 117)	83 (86.4, 97.7, 74.3, 73.4)	0.70
	2 days	nd	<LOD	-
	4 days	nd	<LOD	-
	8 days	nd	<LOD	-
Inj.site muscle (day 1)	4 hours	206 (205, 204, 219, 195)	99.9 (107, 105, 110, 77.7)	-
	2 days	12.3* (nd, 10,1, 14.4, nd)	<LOD	-
	4 days	nd	<LOD	-
	8 days	nd	12.3* (12.5, 12.1)	-
Inj.site skin/fat (day 1)	4 hours	145 (113, 176, 151, 141)	147 (67.9, 212, 211, 98,1)	-
	2 days	13.4[#]	5.8[#]	-
	4 days	40.3* (28.3, nd, 52.2, nd)	15.9 (24.1,3.8,19.7,<LOD)	-
	8 days	50.8* (61.9, nd, nd, 39.6)	22.1* (30.8, 13.4)	-
Inj.site muscle (day 2)	4 hours	1576 (1737, 754, 511, 3303)	937 (980, 611, 649, 1509)	-
	2 days	nd	<LOD	-
	4 days	nd	15.2[#]	-
	8 days	nd	<LOD	-
Inj.site skin/fat (day 2)	4 hours	262 (474, 147, 139, 288)	253 (354, 161, 290, 206)	-
	2 days	17.2* (nd, 13.5, 20.8, nd)	7.1 (3.7, 11.3, 10.0, 3.2)	-
	4 days	66.0 (25.4, 105, nd, 67.6)	25.7 (4.1,57.0, <LOD,16)	-
	8 days	11.0* (12.0, nd, nd, 10.0)	4.5[#]	-

TRR = total radioactive residues
nd = not detected

* = concentrations detected in only 2 animals
# = concentrations detected in only 1 animal
¤ = 3 out of 4 samples not reported due to analytical problems
<LOD = below the limit of detection (1.8µg/kg liver, 2.0 µg/kg kidney, 5.7 µg/kg muscle, 3.0 µg/kg fat and 2.2 µg/kg skin/fat)

The limit of quantification (LOQ) of meloxicam was 10 µg/kg in all tissues.

This residue depletion study was performed according to the requirements of the Rules governing Medicinal Products in the European Union, Volume 8. The study was included in the application submitted for the extension of MRLs for meloxicam to include the target species swine.

Maximum Residue Limits (MRLs)

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

For the elaboration of MRLs the established ADI of 75 µg/person/day was divided in two parts; 45 µg were assigned to edible tissues and 30 µg to the milk. Meloxicam was identified as the marker residue and the ratio of marker residue to total residues retained was 1 for muscle, 0.23 for liver, 0.4 for kidney and 0.75 for milk. Taking into account the distribution of meloxicam residues in edible tissues and a consumption of 300 g muscle, 100 g liver, 50 g kidney and 50 g fat, MRLs for meloxicam.

Meloxicam was 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	Equidae Bovine Porcine	20 µg/kg 65 µg/kg 65 µg/kg 15 µg/kg	Muscle Liver Kidney 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.

The excipients used were either included in Annex II of Council Regulation (EEC) No. 2377/90 for all food producing species. or do not fall within the scope of Council Regulation (EEC) No. 2377/90 in accordance with the CVMP position paper on the definition of substances capable of pharmacological action in the context of Council Directive 81/851/EEC (now Directive 2001/82/EC of the European Parliament and of the Council) with a particular reference to excipients (EMEA/CVMP/046/00-Rev.2).

Based on the results of the submitted depletion study, a withdrawal period of 5 days for milk was accepted by the CVMP during the evaluation of the original application for Metacam 20 mg/ml Solution for Injection. The study documenting tolerance in lactating cows was assessed during the evaluation of the original application for Metacam 20 mg/ml Solution for Injection. Dairy cows were treated with 3 times the recommended dose two weeks before insemination and thereafter on gestation days 9, 35, 105, 203 and 259. No serious adverse reactions occurred and treatment did not influence the common reproductive parameters or the viability of the offspring.

Withdrawal periods

Cattle

Bioequivalence was demonstrated between the commercial formulations of Metacam 5 mg/ml and Metacam 20 mg/ml following subcutaneous injection. Consequently, the residue study performed with Metacam 5 mg/ml solution is relevant for establishing a withdrawal period for Metacam solution for injection 20 mg/ml.

Using the data from the residue depletion study performed in cattle given a single subcutaneous injection of 0.5 mg ^{14}C-meloxicam/kg b.w. (Metacam 5 mg/ml), the established MRL for meloxicam of 65 µg/kg for liver and kidney and the statistical method recommended by the CVMP with a 95% tolerance limit and 95% confidence limit, withdrawal periods of 14.3 and 14.7 days for liver and kidney respectively were estimated. For muscle and injection site muscle residue data do not permit the use of the statistical method. However, eight days after administration the concentrations of meloxicam in muscle are below the limit of detection of the analytical method in all four animals.

There is a large variation in the results for the injection sites. The concentration of meloxicam is below the MRL for muscle in all animals on day 4 and on day 6 and in two out of four animals on day 8. A withdrawal period of 15 days is proposed for meat and offal from cattle administered Metacam 20 mg/ml solution for injection at the recommended dose level.

Both products, Metacam 5 mg/ml and Metacam 20 mg/ml were injected subcutaneously in a bioequivalence study. The total dose volume of each product was given at a single injection site. The results demonstrated that the two formulations were bioequivalent with C_{max} and AUC well within the acceptable bioequivalence range. T_{max} was 8 hours for Metacam 5 mg/ml and 7 hours for Metacam 20 mg/ml. The tolerability of the subcutaneous injection was also assessed. The observation period was 7 days and no local reactions were found at the injection sites.

Pigs

The metabolism and residue depletion study in pigs, using a formulation equivalent to Metacam 20 mg/ml solution for injection, provided data on tissue residues up to 8 days post dosing. Concentrations of meloxicam in liver, kidney and muscle were above the MRLs established for these tissues (65 µg/kg, 65 µg/kg and 20 µg/kg, respectively) only at 4 hours after the last dose. At 2, 4 and 8 days post last dose the concentrations in those tissues were below the MRLs in all animals and also below the limit of quantification (10 µg/kg).

Concentrations of meloxicam in the muscle of the last injection site were highest at the 4-hour sacrifice period with concentrations ranging from 161 to 1509 µg/kg. Two days after the last administration the concentrations of meloxicam were below LOD in all animals. Four days after the last dose the injection site muscle from one animal contained 15.2 µg/kg but the concentrations in the other animals were below LOD. Eight days after the last administration, concentrations of meloxicam in injection site muscle were below LOD in all four animals.

Concentrations of meloxicam in skin/fat from the last injection site ranged between 161 and 354 µg/kg at 4 hours post dose, between 3.2 and 11.3 µg/kg at 2 days and between LOD and 57.0 at 4 days post last dose. Eight days after the last administration concentrations of meloxicam in skin/fat of the injection site were below LOD in three animals and 4.5 µg/kg in one animal.

Since no meloxicam residues could be detected in liver, kidney or muscle at 2, 4 and 8 days except for the injection site muscle of one animal at 4 days (15.2 µg/kg), a statistical analysis according to the approach recommended by the CVMP (EMEA/CVMP/036/95) is not possible.

The residues in the injection sites were also taken into consideration according to the CVMP position paper (III/5933/94). In this study, the residues in the muscle of the injection site were below the MRL

for muscle 2 days after dosing, and remained so at the time-points thereafter. For skin/fat there is no MRL established. The contribution of total residues of meloxicam in skin/fat from the injection sites to the total daily residue intake is small (1 µg at 2 days and 5.3 µg at 4 days, at the most) and at a withdrawal period of 3 days, the calculated total daily intake will be far below the established ADI for meloxicam (75 µg/person) considering the standard food consumption (0.3 kg muscle, 0.1 kg liver, 0.05 kg skin/fat and 0.05 kg kidney).

Results from a further study in lactating sows were also provided by the marketing authorisation holder.

Twelve clinically healthy lactating sows of 1-4 years of age (body weight range 183 – 281 kg) and their litters were assigned to one of three test groups and each sow received two consecutive intramuscular injections at a dose of 0.4 mg/kg body weight. The first injection was given on Day 1, the second on Day 2.

The animals were sacrificed as follows:

Group I: sacrificed at Day 4 (i.e. 2 and 3 days after injection);

Group II: sacrificed at Day 6 (i.e. 4 and 5 days after injection)

Group III: sacrificed at Day 7 (i.e. 5 and 6 days after injection).

Tissue samples from Group I included liver, kidneys, skeletal muscle and injection sites. For Group II and III only injection sites were collected.

At Days 2 and 3 after injection no quantifiable residues residue concentrations were found for kidney, liver and 3 out of 4 skeletal muscle samples. One skeletal muscle sample showed a residue concentration of approximately 11.6 µg/kg (2 days after injection). Meloxicam was above the Limit of Quantification (LOQ, 10 µg/kg) in injection site samples of 3 out of 4 sows. One left injection site sample presented a residue concentration of 76.5 µg/kg at 3 days after injection whereas 3 samples of the right injection site (i.e. 2 days after injection) presented residue concentrations in the range of 18.4 – 164.7 µg/kg.

For sows slaughtered on Day 6 (4 and 5 days after injection), one injection site sample (4 days after injection) presented a residue concentration of approximately 14.6 µg/kg of meloxicam (i.e. below the MRL of 20 µg/kg). In tissue of the remaining 3 sows, meloxicam levels were below the LOQ.

There was no meloxicam above the LOQ in injection site tissue samples from animals slaughtered at Day 7 (5 and 6 days after injection).

The results show that all residues of meloxicam in liver, kidney, skeletal muscle and injection sites were below their MRL values 4 days after the second injection.

Given these additional data, a withdrawal period of 5 days was considered acceptable.

Horses

Intravenous and oral pharmacokinetic study with meloxicam in the horse

The aim of the study was to determine the absolute bioavailability of meloxicam in horses, to determine the influence of feeding conditions on the rate of meloxicam absorption, to document meloxicam kinetics in steady state conditions and to describe urinary meloxicam excretion.

Each group of four horses (2 adult males and 2 females of various breeds; weighing 350 to 606 kg) was dosed with either an oral (Metacam 15 mg/ml oral suspension) or intravenous (Metacam 2 %

solution for injection) nominal dose of 0.6 mg meloxicam/kg bodyweight. Horses were fasted overnight prior to dosing and fed 2 hours post dose.

After a washout period of 6 weeks eight horses received a daily oral dose of 0.6 mg meloxicam/kg b.w./day (nominal dose) for 14 consecutive days. The horses were fed immediately after dosing and not fasted overnight.

In plasma the concentrations of meloxicam were determined by an HPLC procedure with UV detection. Urine samples were analysed for meloxicam using an HPLC method with electrospray mass spectrometry detection.

After a single intravenous dose, plasma kinetic parameters were evaluated. Kinetic parameters were also determined after single oral doses to fasted horses and to fed horses.

The oral bioavailability was high in both fasted and fed horses and not statistically different to each other. The Mean Residence Time, the Mean Absorption Time and T_{max} were significantly higher in fed than in fasted animals. C_{max} was significantly lower in fed than in fasted animals. This suggests that the rate of absorption of meloxicam is slower in the presence of food whereas the absolute bioavailability remains unchanged.

The plasma kinetic parameters obtained for the multiple oral administration of meloxicam were presented. The plasma concentrations obtained over 14 days of administration fitted a two-compartment model. The low accumulation factor suggests that meloxicam does not accumulate when administered daily.

Urinary concentrations of meloxicam remained fairly constant from day 0 to Day 13 of administration and declined below the limit of quantification (20 ng/ml) within 3 days after the final dose. The data indicates that the absorption of meloxicam is rapid and that there is no accumulation of the substance.

Depletion of residues

Twelve horses (6 male and 6 female weighing 470-542 kg prior to dosing) were randomly assigned to 3 groups of 4 animals (2 male and 2 female). Each group received an oral nominal dose of 0.6 mg meloxicam/kg bodyweight (Metacam 15 mg/ml oral suspension) once daily for 14 consecutive days. The doses were administered orally in a small portion of each horse's food ration After the final administration one group was sacrificed at 12, 24 and 48 hours post last dose. Samples of liver, kidneys and muscle from the hind quarter were analysed for residues of meloxicam using a validated HPLC procedure. The actual daily doses administered to each horse were in the range of 0.600-0.605 mg/kg bodyweight. The concentrations of meloxicam measured in tissues are presented in table 1.

Table 1. Concentrations of meloxicam in the tissues of horses treated orally once daily with 0.6 mg meloxicam/kg b.w. for 14 consecutive days. Results for mean and individual values in µg/kg.

Withdrawal time (h)	**Liver**	**Kidney**	**Muscle**
12	98.3 146 126 90.4	1350 814 1740 1200	20.7 <LOQ 35.1 17.1
Mean	**115**	**1280**	**18.2**
24	69.1 70.4 47.7 45.4	621 454 450 553	<LOQ ND <LOQ <LOQ
Mean	**58.2**	**520**	**<LOQ**
48	<LOQ <LOQ <LOQ <LOQ	43.9 76.3 74.8 30.2	ND ND ND ND
Mean	**<LOQ**	**56.3**	**ND**

LOQ = Limit of quantification (20 µg/kg for liver and 10 µg/kg for muscle)
ND = below limit of detection (3.3 µg/kg for muscle)

This residue depletion study was performed according to the requirements in Volume 8 of the Rules Governing Medicinal Products in the European Community.

Maximum Residue Limits

An ADI of 1.25 µg/kg b.w. was previously established by the Committee for Veterinary Medicinal Products (CVMP) for meloxicam.

Meloxicam was 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	Equidae Bovine Porcine	20 µg/kg 65 µg/kg 65 µg/kg 15 µg/kg	Muscle Liver Kidney Milk	

The excipients included in Metacam 20 mg/ml solution for injection (according to the qualitative and quantitative composition) were either included in Annex II of Council Regulation (EEC) No 2377/90 or out of scope of this regulation and do not present any risk for the consumer.

Withdrawal periods

It is recognised that the pharmacokinetic studies with meloxicam in the oral suspension in horses show a high but not a complete (i.e.100 %) bioavailability. After a single oral dose of 0.6 mg/kg the bioavailability was 85.3 % in fasted horses and 95.9 % in fed horses. After oral administration of 14 daily doses of 0.6 mg/kg the bioavailability was 97.6 %.

The Committee considered that it was appropriate to establish the same withdrawal period as for the oral suspension but with a safety margin of 2 days, resulting in a withdrawal period of 5 days (also the withdrawal period established for Metacam 20 mg/ml solution for injection to pigs).

Routine Analytical Methods

The proposed routine method for residue surveillance is an HPLC procedure, presented in the ISO 78/20 format and validated for milk, muscle, liver and kidney according to Volume VI of the Rules Governing Medicinal Products in the European Community. The limits of quantification are 2.5 µg/kg for milk and 10 µg/kg for muscle, liver and kidney. The limits of detection are 1.5 µg/kg for milk, 2 µg/kg for muscle, 3 µg/kg for liver and 1.5 µg/kg for kidney.

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 8 of the Rules Governing Medicinal Products in the European Union. 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.
A 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 is based on the fully validated method for bovine tissues and met 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.

EFFICACY ASSESSMENT

Pharmacokinetics

Pigs

One study documenting the pharmacokinetics of meloxicam in pigs after administration of daily intramuscular doses for two consecutive days is submitted.

^{14}C-meloxicam metabolism and residues in tissues following intramuscular administration to pigs

A formulation of meloxicam corresponding to Metacam 20 mg/ml was injected intramuscularly to pigs at the dose of 0.4 mg/kg on two consecutive days. The animals were sacrificed in groups of 4 at 4 hours and at 2, 4 and 8 days after the second dose. Blood samples were collected at various times after dosing from the animals sacrificed after 4 days and faeces and urine were collected at 24 hourly intervals.

Total radioactivity and the concentration of meloxicam were measured in plasma and major pharmacokinetic parameters were calculated. The radioactivity increased to a mean maximum concentration of 1662 ng equivalents/ml at 1 hour post dosing and declined thereafter to reach a mean of 19 ng equivalents/ml at 96 hours.

Meloxicam was analysed by a fully evaluated HPLC method. The concentration reached a maximum of 1856 ng/ml after 1 hour and declined to a mean of 156 ng/ml at 12 hours. Meloxicam could not be detected in plasma in three of the four animals beyond 12 hours and in none of the animals beyond 24 hours. The mean terminal half-life was calculated to 2.5 hours.

Tolerance in the target species

Cattle

Safety in calves was earlier documented with Metacam 5 mg/ml. Due to bioequivalence of both formulations, these studies are also relevant for the safety of Metacam 20 mg/ml. A study of the safety of Metacam 20 mg/ml after intravenous administration was also performed. The results from these studies showed that daily intravenous injections of 3 times the recommended dose for up to 5 consecutive days caused no serious adverse reactions. However, mild erosions were found in the abomasal mucosa in single animals (including controls).

It has been demonstrated that meloxicam at doses of 1.5 mg/kg (three times the recommended clinical dose) has no effect on reproduction of cows as well as no foetotoxic/teratogenic effect when given multiple times before and during pregnancy.

Metacam 20 mg/ml is intended for intravenous and subcutaneous administration. The results of the bioavailability studies show that the bioavailability of meloxicam is similar after both routes of administration, and thus the animals are exposed to the same total amount of drug after both intravenous and subcutaneous injection. The local tolerance of the recommended dose was evaluated in separate studies.

A total of 556 calves were injected by the subcutaneous route with 0.5% solution in the studies included in the original dossier for Metacam. In some studies, transient local reactions were found in about 30% of the treated animals. A comparison between the two injection formulations were made in one of the pharmacokinetic studies. No serious general or local adverse reactions occurred after meloxicam treatment.

Pigs

Meloxicam (Metacam 2% solution for injection) target animal tolerance study in pigs.

Twenty-four pigs, aged 5-6 months, and weighing from 49 kg to 60 kg were randomly allocated to four groups. The groups were treated with 0, 0.4, 1.2, and 2.0 mg/kg b.w. intramuscularly once daily for 6 consecutive days.

The animals were observed several times daily for signs of toxicity. Bodyweight, food and water consumption, heart rate, respiratory rate and rectal temperature were recorded. No signs of illness

occurred and all studied parameters were similar in all groups. Autopsy revealed no changes that could be related to treatment. However, moderate inflammatory reactions were found at the injection sites of the animals treated with the highest doses. The reactions after the recommended dose, 0.4 mg/kg b.w. were similar to those after injection of physiological saline.

Horses

Studies were previously submitted for the 15 mg/ml oral suspension for horses. Horses were treated orally with 1X, 3X and 5X the recommended dose (0.6 mg/kg b.w.) for 42 days, i.e. 3 times the recommended treatment period. The recommended dose was well tolerated, while treatment with 3X and 5X the recommended doses for 3 times the recommended period induced serious reactions such as severe weight loss, oedema, ulcerations of the mucosa of the gastrointestinal tract and papillary necrosis of the kidney. The lesions are characteristic for that class of compounds.

As the bioavailability of the oral suspension is high (85-97%), the results were also relevant for Metacam 20 mg/ml solution for injection.

Intravenous bolus doses of up to 2 mg/kg were well tolerated in the dose finding study however safety was not demonstrated in pregnant mares and foals but the age limit for the latter was justified. In order to add an additional safety span, Metacam may only be used in foals older than 6 weeks.

Preliminary results from an ongoing efficacy study show Metacam and a comparator product to be well tolerated as local transient swellings at the injection site occurred only in single animals in both treatment groups. One case of anaphylactoid reaction occurred in the Metacam group and an appropriate statement was included in the SPC.

Pregnancy and lactation

Studies in rats and rabbits produced no evidence of a teratogenic effect or of an influence on fertility. However, a slight prolongation of the gestation period was observed in rats. Later studies showed that Metacam can be safely used in pregnant cows.

Reproductive data in pigs were submitted. A total of 53 sows were available for evaluation, 25 in the Metacam group and 28 in the placebo group. The sows were treated 73 days before insemination (range 5 – 114 days). The total number of piglets per litter, the number born alive, born dead, malformed or mummified did not differ between the groups.
A further study, "Tolerance of Meloxicam in Piglets¨ (Study P 01 BIVI009), demonstrating safety in piglets was submitted. Ten lactating sows with body weights ranging from 126 kg to 263 kg were included in this study. The number of piglets per litter varied from 7 to 11. The sows were divided into two equal groups, one group was treated with Metacam, 0.4 mg/kg b.w., on two consecutive days, the other group was treated with placebo.

Blood was collected for haematology and clinical chemistry from the sows and piglets on day 1 prior to treatment and from the piglets also on day 7. Clinical examination of the piglets was performed twice daily until day 7 and the following parameters were recorded: signs of diarrhoea and dyspnoea, nutritional state, suckling behaviour, and general condition.

No significant differences between the groups of piglets were found regarding body weight, clinical signs haematology and clinical chemistry. Two piglets in each group (one in each group) died during the study. Necropsy revealed purulent arthritis in one animal, the other was crushed by its mother.

Safety was therefore satisfactorily documented in pregnant sows and in the piglets of treated sows.

Clinical Studies

Cattle:
Diarrhoea in Calves

The aim of the study was to evaluate the clinical efficacy of N-butylscopolamine bromide and meloxicam either given alone or in combination to calves showing signs of diarrhoea. A negative control group, treated with saline, and a positive control group treated with N-butylscopolamine + metamizole were included. The N-butylscopolamine + metamizole combination is approved for the treatment of diarrhoea in some Member States. All animals were given appropriate fluid therapy (for 2-3 days) and antibiotic treatment (gentamycin 5 mg/kg on day 1 and optionally on day 2). Clinical scores including diarrhoea scores were compiled from a number of relevant variables. The analyses showed consistent results after initiation of treatment. The groups differed significantly at each time point in all models in favour of Metacam, alone or in combination. Eighty per cent of the animals in the Metacam group were judged as normal after 48 hours, compared with 37% in the control group.

All calves were also treated orally with an electrolyte solution at 70 g/50 kg on days 1 and 2 and optionally also on day 3. A total of 501 calves were recruited to the study. The mean age of the animals was 2 weeks. A detailed summary of the animal management on the farms was provided. Clinical examinations were performed immediately before treatment, after one hour and after 6-8 hours and thereafter at 24 and 48 hours after treatment. The primary efficacy parameters were the clinical diarrhoea score and the clinical index score which in addition to the clinical diarrhoea score also included the scores for behaviour, feed intake, rectal temperature, respiratory rate, heart rate and general condition. There were small but statistically significant differences between the groups prior to treatment. Changes from baseline were evaluated statistically to adjust for the differences prior to treatment.

All groups responded to therapy. The statistical evaluation showed significant differences between the control group and the treated groups.

In cases of acute diarrhoea, the major clinical benefits would be achieved within the first 48 hours following treatment. If treatment is not successful, the condition of the animal deteriorates rapidly and parenteral fluid therapy is necessary.

The difference between the control group and the treated groups with regard to clinical score was statistically significant after 48 hours. Eighty per cent of the animals in the Metacam group was judged as normal after 48 hours, compared with 37% in the control group.

Mastitis in cattle

Clinical efficacy of a single intravenous injection of meloxicam (Metacam 20 mg/ml solution for injection for cattle) in combination with antibiotic therapy for the treatment of acute mastitis in cattle.

This double-blinded, controlled study was performed at 12 different centres in Germany and included a total of 240 cows suffering from acute febrile mastitis. The cows were recruited from 144 different farms. The inclusion criteria were: rectal temperature $\geq$40°, clinical signs of mastitis in one quarter, moderate to severe impaired general condition, a daily milk yield of at least 5 litres, and available data of the actual milk yield. The cows had to be treated by the veterinarian within 2 hours after he was called by the farmer.

The number of cows recruited by the different investigators varied from 8 to 40.Detailed information on farm management is given. Most of the cows were milked twice daily.

All cows were examined clinically before the initiation of treatment, milk was sampled for bacteriological examination and for somatic cell count by the Fossomatic method and the California

Mastitis Test (CMT). The cows were randomly allocated to two groups. All animals received an intramuscular injection of cefquinome (Cobactan) and intramammary treatment with cefacetril (Ubrocef) of the affected quarter. The antibiotics were given at the recommended doses. The intramuscular injection could be repeated on day 2 if deemed necessary ,and the intramammary treatment could be repeated on days 2 and 3.

In addition to the antibiotic therapy, the cows in one group were given a single intravenous injection of Metacam 20 mg/ml at a dose of 0.5 mg/kg b.w., the cows in the other group were treated intravenously with flunixin, 2.2 mg/kg b.w. for up to 5 days.

Clinical examination was performed on day 1 (immediately before treatment) and on days 2, 3, and 8. The following general clinical parameters were recorded: rectal temperature, respiratory rate, heart rate, ruminal activity and feed intake. The sum of these parameters was defined as the general condition.

The following local parameters were scored: the CMT test, milk appearance, milk yield, symptoms of severity of inflammation.

The primary parameter for conclusion on efficacy was the clinical sum score (CSS) that was defined as the sum of the scores for general condition, milk appearance and symptoms of severity of inflammation (maximum 10, minimum 0 score points).

Four cows, two in each group, were excluded from the final evaluation because of protocol violations.

At initiation of treatment the two groups were fully comparable regarding age, body weight, lactation number, days in lactation, daily milk yield and CSS.

All individual parameters forming the CSS decreased during the course of the study and the statistical analysis showed non-inferiority for meloxicam versus flunixin.

Both the Fossomatic method and the CMT test were used for the somatic cell count. The statistical analysis showed good correlation between the two methods.

The mean CSS during the study period was as follows:

	Metacam group	**Flunixin group**
Day 1	8.1	8.0
Day 2	4.1	4.6
Day 3	2.3	2.9
Day 8	0.8	0.7

The CSS on days 2 and 3 differed significantly in favour of meloxicam. The number of cows available for evaluation on day 8 was 105 in each group.

The longer study period in comparison with the earlier submitted study made it possible to obtain information on clinical relapses. A relapse was considered to have occurred if clinical symptoms of mastitis in the same quarter occurred 48 hours after the last treatment, rectal temperature was 40° or higher or the clinical case required additional treatment.

The number of relapses was 10 in the meloxicam group and 2 in the flunixin group. This difference appeared to be statistically significant. E. coli was the most common infection (33%), Strept.spp (uberis, agalcatiae, dysgalactiae) were isolated from 27% of the cows and Staph. aureus from 14%. Infection could not be detected in 12% of the samples.

The cows were grouped according to infectious agents. One group included cows infected with what was defined as major pathogens (E.coli, Str.dysgalactiae, Str.agalactiae, Str.uberis and Staph.aureus). All other bacterial species was defined as minor pathogens. This group also included cows where no infection was detected (12%) and cows with a mixed infection.

The number of cows infected with major pathogens was 81 in the meloxicam group and 85 in the flunixin group. The CSS was reduced to the same extent by meloxicam and flunixin. The mean CSS was 8.0 in both groups and was reduced to 2.3 and 3.0, respectively, on day 3.

The number of cows infected with minor pathogens was 37 in the meloxicam group and 33 in the flunixin group. Meloxicam and flunixin showed similar efficacy also in this group. The mean CSS was 8.1 and 7.8, respectively, on day 1 and was reduced to 2.4 and 2.5 respectively, on day 3.
The secondary efficacy parameters showed significant reduction in severity, i.e. decreased rectal temperature, respiratory rate and heart rate. The ruminal activity was increased after treatment. No statistically significant differences between meloxicam and flunixin groups were observed.

Severity of inflammation in the affected quarter, which is a component of CSS, was most intense Day 1 prior to treatment. A significantly better result was obtained with meloxicam at Day 3 with 42 cows (37%) with the lowest score compared to 16 cows (14%) in the flunixin group.

No adverse reactions occurred.
Pigs

Evaluation of the therapeutic efficacy of three doses of meloxicam in an i.v. endotoxin model in pigs.

An established model was used to study the effects of meloxicam on the clinical symptoms induced by intravenous injection of E. coli endotoxin. Thirty-two pigs with a mean weight of 34.1 $\pm$ 3.3 kg were allocated to four groups of 4 males and 4 females. All animals received an intramuscular injection of meloxicam at the doses 0, 0.2, 0.4 and 0.8 mg/kg b.w one hour prior to the intravenous injection of E. coli endotoxin O55:B5 at a dose of 4µg/kg body weight. The following clinical parameters were recorded and scored for a period of 24 hours after the endotoxin injection: rectal temperature, general behaviour, respiratory rate, local symptoms, coughing, diarrhoea, position, shivering, vomiting and hyperexitability/hyperesthesia.

Blood for analysis of thromboxane B_2 was collected at predetermined intervals. The animals in all groups responded to the endotoxin injection with increased rectal temperature. The temperature increased to 40° or higher and meloxicam appeared to have no antipyretic effect in this model study.

The clinical symptoms were reduced by meloxicam, but the only scored parameter that was significantly reduced by meloxicam was shivering. The effect was most pronounced in the groups receiving 0.4 and 0.8 mg/kg b.w.

The observed clinical symptoms were presented as the total clinical score (TCS), defined as the sum of the scores for each individual parameter. AUC was calculated for each group. All meloxicam treated groups showed significantly lower AUCs than the control group, and no significant differences were found between the dose groups 0.4 and 0.8 mg/kg body weight. Based on the TCS a maximum effective dose of 0.43 mg/kg b.w. was estimated statistically using the linear spline model.

Meloxicam reduced the increase in thromboxane B_2 significantly, the response appeared to be dose related.

Meloxicam at a concentration of 5 mg/ml was used in this study and no adverse reactions occurred.

The required data have been submitted. The theory of the linear spline model was given and the use of the model was described. The dosage was established by using ¨total clinical score¨ and that rectal

temperature was only one component of this sum score. Further, the dose 0.2 mg/kg showed a statistically significant improvement of the¨total clinical score¨.

Clinical efficacy of meloxicam (Metacam) in sows with puerperal septicaemia and toxaemia.

The aim of this study was to compare the effects of Metacam and flunixin in sows suffering from the MMA syndrome. The study was blinded and performed at five different centres in Germany.

A total of 200 sows were recruited for the study. All animals had given birth to at least 5 live piglets and showed a slightly disturbed general demeanour, a reduction in feed intake by about 1/3, a slight vaginal discharge, and/or slight inflammation of the mammary gland and a rectal temperature of 40° or higher.

All animals were treated with enrofloxacin i.m. at the dose 2.5 mg/kg b.w. and a long-acting oxytocin formulation on day 1. Half of the animals were also treated with Metacam, 0.4 mg/kg b.w. and the other half with flunixin, 2 mg/kg b.w. The enrofloxacin injection was repeated on day 2. Depending on the clinical response, treatment with Metacam and Flunixin could be repeated on day 2.

Clinical examination was performed prior to treatment on day 1, and thereafter on days 2, 3, 4 and 8. Rectal temperature was recorded daily and the following parameters were scored: respiratory rate, feed intake, general demeanour, vaginal discharge, number of mammary glands affected, degree of inflammation of the most severely affected gland, milk flow and nursing behaviour. Each litter was examined and weighed. Milk and vaginal discharge were collected for bacteriological examination.

The primary parameter for conclusion on efficacy was the clinical index score on day 2. The clinical index score was defined as the sum of the scores for each individual parameter. Ninety-four sows in the Metacam group and 93 in the flunixin group could be evaluated. The mean age of the animals was 24.7 months and 26.8 months, respectively. The mean number of piglets on day 1 was 11.1 and 10.8, respectively.

The major diagnosis (>55%) in each group was mastitis. The bacteria most often isolated from the milk samples were Staphylococcus spp, E.coli and Streptococcus spp. Twenty-five per cent of the staphs. showed resistance against enrofloxacin. The scores for each individual parameter were almost identical in both groups on day 1. The clinical index score (mean $\pm$SD) for each study day is given in the table.

The statistical evaluation showed a significant non-inferiority of Metacam compared to flunixin. The incidence of relapses was similar in both groups, 14% and 15%. respectively. A relapse was considered to have occurred if the clinical condition deteriorated on day 8 compared to day 4 as seen by an increase of the clinical index score. Until day 8, 10.4% of the piglets in the Metacam group had died and 12.0% in the Flunixin group. For diseased litters, mortality rate in the meloxicam group was significantly lower than in the flunixin group, 14.0% vs. 31.7%.

One sow of the Flunixin group and two sows of the Metacam group died or were euthanized during the study. One further sow of the Metacam group was euthanized after the study was completed. Three of the sows were autopsied and the autopsy reports were submitted. Autopsy revealed that one of the sows had died of streptococcal septicaemia and the isolated bacteria were resistant to enrofloxacin. Further, the sow showed gastric ulceration, but the age of the lesions was not given by the pathologist.

The presented study complied with relevant Directives and guidelines.

Clinical efficacy of meloxicam (Metacam) in swine with non-infectious locomotor disorders.

The study was performed at 5 different centres in Germany. Two hundred and twenty swine with non-infectious locomotor disorders were recruited for this blinded, placebo controlled study. The age of the animals varied from 2 to 48 months and the weight ranged from 20 to 300 kg. The animals were randomly allocated to two groups, a placebo group and a treatment group. Pregnant and non-pregnant sows and gilts were the dominating categories in both groups, the number of fattening pigs was 23 in the Metacam group and 20 in the control group. The pigs of the Metacam group were treated with 0.4 mg/kg b.w. i.m. on day 1, if it was deemed necessary, treatment could be repeated on day 2.

The duration of symptoms was about 3 days in both groups. Clinical examination was performed on days 1, 2, 3 and 4. Leg weakness, distorsion and arthropathy were the major diagnoses in both groups.

The following parameters were scored on each of the four trial days: rectal temperature, feed intake, behaviour, lameness at rest and lameness at walk. The primary parameter was the ¨the clinical lameness score¨, which was defined as the sum of the scores for lameness at rest and lameness at walk. One hundred and three animals could be evaluated in the Metacam group on day 4 and 106 in the control group.

Prior to initiation of therapy there were no differences between the groups, the clinical lameness score was 6.8 in the Metacam group and 6.3 in the control group. On day 4, the mean score had improved to 3.5 in the Metacam group and 4.7 in the control group. The difference between the groups was statistically significant on days 3 and 4. No clinical symptoms were recorded for 49% of the animals of the Metacam group on day 4, the corresponding figure for the control group was 27%. A comparison of the changes versus baseline between the groups showed significant differences on days 2, 3 and 4.

The rectal temperature remained within normal limits during the trial. Feed intake improved in both groups, however, there were significant differences between the groups in favour of Metacam for all time points after initiation of therapy. Additional treatment with Metacam on day 2 was given to 46% of the animals and placebo was given to 73%, the difference was statistically significant. The investigators were allowed to change therapy if the condition deteriorated, but these animals were excluded from the evaluation. Therapy was changed in three pigs in the Metacam group and in one pig in the control group. A single adverse event was reported for one animal of the placebo group. The pig showed pronounced swelling at the injection site on day 2. The swelling disappeared without treatment. The conclusion of the study was that Metacam is safe and efficacious in pigs suffering from non-infectious locomotor disorders.

An established endotoxin model was used in the dose finding study. Pretreatment with meloxicam at the doses 0.4 mg/kg and 0.8 mg/kg reduced, but did not abolish the clinical signs induced by endotoxin. The dose was based on the reduction of the total clinical score.

Metacam showed significant better effect than placebo when used for treatment of non-infectious locomotor disorders. The primary parameter in this study was the clinical lameness score, defined as the sum of the scores for lameness at rest and lameness at walk.

The effect of Metacam was equivalent to that of flunixin when used for treatment of the MMA syndrome in sows.

Horses
Clinical Studies

The proposed dose, 0.6 mg/kg b.w., was based on the results of the intravenous dose finding study. This study was assessed previously. The efficacy of the dose was confirmed in 3 field studies which were submitted with an earlier application.

The effect of Metacam was compared with that of vedaprofen in all three studies. The number of horses included in the studies was sufficient to allow valid conclusions. Treatment with Metacam was found to give equal or better results than vedaprofen treatment.

Plasma concentrations were of the same order after the two routes of administration (oral and i.v.). The major efficacy parameters in the intravenous dose finding study were lameness score and stride length. A statistical evaluation was performed 8 hours after treatment. Raw data for later time points were submitted, but no statistical calculations were performed. A statistical analysis was conducted at the time point 24 hours post injection using the t-test for paired data and the Wilcoxon signed rank test. Both tests showed that the stride length at 24 hours differed significantly from the pre-treatment value. Lameness was borderline significant from the pre-treatment value when the non-parametric test was used, but differed significantly with the t-test.

Clinical efficacy of meloxicam (Metacam) in horses for relief of pain associated with colic

The objective of the study was to evaluate the clinical efficacy of Metacam 20 mg/ml at a dose of 0.6 mg/kg b.w. for relief of pain associated with equine colic under practical field conditions. The study was designed as a positive controlled, double blinded, randomised multicentre study to demonstrate non-inferiority of Metacam 20 mg/ml in comparison to vedaprofen 50 mg/ml. The study was conducted at 12 different sites in Germany.

A total of 276 horses with clinical signs of colic were recruited to the study. The horses were randomly allocated to two treatment groups. One group was treated with Metacam 0.6 mg/kg b.w. and vedaprofen placebo, the other group was treated with vedaprofen 2 mg/kg b.w. and Metacam placebo. All treatments were given intravenously.

The horses were examined clinically before and during 24h after treatment.

The primary parameter for evaluating the efficacy of treatment was the score for colic symptoms. The pain score was considered as a secondary parameter.

Spastic colic was diagnosed in 49% of the horses, constipation in 31% and meteorism in 9%.
One hundred and thirty-four horses in the Metacam group and 135 in the vedaprofen group were available for evaluation.

All horses responded rapidly to treatment. The pre-treatment colic score was 2.9 in both groups. The score had decreased to 2.0 in the Metacam group and to 1.9 in the vedaprofen group after 15 min. Thereafter the score decreased at each time point and reached 1.1 in both groups after 24 hours.

The pre-treatment pain score was 4.10 and 4.12, respectively, and decreased to 1.93 in the Metacam group and to 1.78 in the vedaprofen group after 15 min. The scores declined continuously and were 0.08 and 0.07, respectively, after 24 hrs.

For the primary variable non-inferiority of Metacam in comparison to vedaprofen was demonstrated.

One horse in the Metacam group showed signs typical for anaphylactic shock within one minute after the injection. The animal was given adrenalin and a depot corticosteroid and recovered after 10 min.

Lack of efficacy was observed in one horse in the vedaprofen group. The diagnosis was torsio coli.
The horse worsened after treatment and died after one hour. No autopsy was performed as the owner denied such procedures.

Local reactions at the injection site occurred in 2 horses in the Metacam group and in 3 horses in the vedaprofen group.

Neither Metacam nor vedaprofen appeared to mask cases needing surgical intervention. Three horses in each group underwent surgery.

Risk-Benefit Assessment

The safety of Metacam 20 mg/ml in pregnant and lactating cows has been demonstrated. No effects of Metacam 20 mg/ml on the reproduction of cows and development of offspring were found.

An Acceptable Daily Intake (ADI) of 1.25 µg/kg b.w. (i.e. 75 µg/person) was established by the CVMP for meloxicam by applying a safety factor of 100 to the Lowest Observed Effect Level (LOEL) of 0.125 mg/kg for effects of the gestation length in a reproductive toxicity study in Sprague Dawley rats. MRLs for meloxicam were established for the bovine species as 20 µg/kg - muscle; 65 µg/kg - liver; 65 µg/kg - kidney and 15 µg/kg – milk. Based on these MRL values, the daily intake of meloxicam from residues in milk and bovine tissues will represent about 97% of the ADI.

Bioequivalence was demonstrated between the commercial formulations of Metacam 5 mg/ml and Metacam 20 mg/ml following subcutaneous injection. In the residue depletion study in cattle a single subcutaneous injection of 0.5 mg ^{14}C-meloxicam/kg b.w. (0.5% solution of Metacam) was administered. Using the statistical method recommended by the CVMP with a 95% tolerance limit and 95% confidence limit, withdrawal periods of 14.3 and 14.7 days for liver and kidney respectively are estimated. Residue data for muscle and injection site muscle do not permit the use of the statistical method. However, eight days after administration the concentrations of meloxicam in muscle are below the limit of detection of the analytical method in all four animals. The concentration of meloxicam at the injection site is below the MRL for muscle in all animals on day 4 and on day 6 and in two out of four animals on day 8.

A withdrawal period of 15 days was considered appropriate for cattle meat, offal and of 5 days for pig meat and offal.

The pharmacokinetics of Metacam 5 mg/ml after intravenous and subcutaneous injection has previously been sufficiently documented in calves both after single and repeated doses using radio-labelled meloxicam. The elimination half-life was 24 - 26 hours. The bioavailability was high after subcutaneous injection (92%).

The safety of Metacam has previously been studied in calves and young cattle. The results for those studies showed that daily intravenous injections of 3 times the recommended dose for up to 5 consecutive days caused no serious adverse reactions. Mild erosions were found in the abomasal mucosa in some animals including controls. Subcutaneous injection was occasionally associated with transient swelling at the injection site (less than 10% of the animals included in the previously assessed clinical studies).

For the diarrhoea claim, one clinical non-blinded study was submitted involving 501 calves allocated to one of 5 groups given N-butylscopolamin-bromide, Metacam, N-butylscopolamin-bromide + Metacam, N-butylscopolamin-bromide + metamizole or saline. All animals were given appropriate fluid therapy (for 2-3 days) and antibiotic treatment (gentamycin 5 mg/kg day 1 and optionally on day 2). Clinical scores including diarrhoea scores were compiled from a number of relevant variables There were significant differences between the groups prior to treatment with the highest disease scores in the groups given Metacam.

In cases of acute diarrhoea, the major clinical benefits would be achieved within the first 48 hours following treatment. If treatment is not successful, the condition of the animal deteriorates rapidly and parenteral fluid therapy is necessary.

The difference between the control group and the treated groups with regard to clinical score was statistically significant after 48 hours. Eighty per cent of the animals in the Metacam group was judged as normal after 48 hours, compared with 37% in the control group.

The recommended indication was therefore for use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in calves and young, non-lactating cattle and for use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle. The respiratory indication was subsequently extended to use in cattle.

Mastitis
Metacam 20 mg/ml was previously approved for use as single treatment in cattle and is well tolerated. The evaluation of the quality part of the dossier was also carried out previously.

MRLs have been established previously by the CVMP in accordance with Council Regulation (EEC) 2377/90 as amended.

Efficacy was documented in a double-blind, controlled study performed at 12 different centres which included a total of 240 cows suffering from acute febrile mastitis. It was demonstrated that meloxicam and flunixin were effective to a similar extent.

The indication "For adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy." is considered to be supported.
Pigs

The proposed dose in pigs was 0.4 mg/kg b.w. based on the results from a submitted dose titration study. The results of the pharmacokinetic studies showed that the elimination half-life was significantly shorter in swine than in cattle (2.5 hours vs 26 hours), permitting a treatment duration proposal. The marketing authorisation holder proposes that based on the clinical response, swine can be treated for two consecutive days.

Metacam 20 mg/ml appeared to be well tolerated in pigs, no serious adverse reactions occurred in the tolerance study or in the clinical studies. Swelling at the injection sites were observed after injection of 3 and 5 times the recommended dose, but not after injection of the recommended dose.

MRLs for swine were previously established by the CVMP. The submitted residue depletion studies were performed in compliance with the current guidelines and the withdrawal period of 5 days was considered appropriate.

The clinical efficacy of Metacam was documented in two studies. Metacam was found to give significantly better results than placebo when used for the treatment of non-infectious locomotor disorders. The study included both fattening pigs and pregnant and non-pregnant sows and gilts.

Metacam was also proposed for the treatment of the MMA syndrome in sows. The submitted documentation was adequate to support the claim for adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy.

Line extension to Horses

Metacam 20 mg/ml solution for injection is indicated for use in the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses. The product is presented in colourless glass injection vials of 50 and 100 ml.

Metacam 20 mg/ml solution for injection is intended for initial treatment of non-infectious musculo-skeletal disorders. A single intravenous injection shall be given, the treatment may then be continued by Metacam 15 mg/ml oral suspension. The therapeutic index is narrow, but Metacam 20 mg/ml appears to be safe when properly used. The recommended dose is 0.6 mg/kg b.w., but single intravenous bolus doses up to 2 mg/kg b.w. were well tolerated in the dose finding study.
The testing specifications for the active ingredient, for the excipients and for the package materials were considered acceptable.

An ADI of 1.25 µg/kg b.w.. (i.e. 75 µg/person) for meloxicam was previously established by the CVMP by applying a safety factor of 100 to the LOEL of 125 mg/kg b.w. for effects on gestation length in a reproductive toxicity study in Sprague dawley rats.
The CVMP considered it appropriate to establish a withdrawal period of 5 days.
Metacam 20 mg/ml solution for injection is intended for treatment of individual animals and no herd treatment will occur. The submitted Phase I Assessment of ecotoxicity was therefore considered to be sufficient.
The marketing authorisation holder referred to the previously submitted efficacy studies and to the fact that the dose titration study was done using intravenous injection. Furthermore, the bioavailability of the oral suspension is high and consequently the efficacy data obtained with the oral suspension are relevant also for the formulation intended for injection. This argumentation was considered acceptable.

Metacam 20 mg/ml is also indicated for the relief of pain associated with equine colic. In the submitted study colic symptoms were the primary parameter and pain was considered as a secondary parameter.

IV METACAM 5 MG/ML SOLUTION FOR INJECTION FOR DOGS AND CATS

Metacam 5 mg/ml Solution for Injection is presented in 10 and 20 ml vials with 15% ethanol as preservative. The initiation of treatment in dogs can be performed using subcutaneous administration at a dose of 0.2 mg/kg body weight. Metacam 1.5 mg/ml oral suspension may be used for continuation of treatment at a dosage of 0.1 mg meloxicam/kg body weight, 24 hours after administration of the injection in dogs.

Quality assessment

Composition

Qualitative Composition	Quantitative composition mg/ml	Reference to analytical quality
Active Substance(s) Meloxicam	5.0	BP
Ethanol	150	Ph.Eur.

Container

Colourless glass injection vial, glass type I, with a stopper of ethylene propylene norbornene terpolymer rubber and aluminium cap. Filling volume 10 ml. The vials and stoppers satisfy the requirements of Ph. Eur.

The use of the product in cats as well as dogs is expected to increase the number of individual doses likely to be withdrawn from each 10 ml vial. The marketing authorisation holder has demonstrated that the integrity of the closures (particularly in terms of fragmentation and self-sealability) will be maintained when the closures have been punctured the average number of times likely to be encountered in practice.

DESCRIPTION OF METHOD OF PREPARATION

Manufacturer of the finished product (all steps) including control tests on the finished product: Labiana Life Sciences S.A., Venus 26,. Can Parellada, 08228-Les Fonts Terassa, Barcelona, Spain.

The typical batch-size is 200 or 1025 litres. The manufacturing formula for both a 200 litre and for a 1025 litre batch was presented. The successive addition of ingredients was shown in a flow- chart over the manufacturing process. Standard manufacturing procedures are used. The bottles are filled under nitrogen as a routine procedure, which corresponds to current technical standards. The product is sterilised in the container at 121°C for 15 minutes. In-process controls include check of pH, filter integrity test, extractable volume, autoclave parameters and particulate contamination/leakage.

The principal manufacturing process has been satisfactorily investigated.

Validation of the process

The product is manufactured using a standard process, which employs conventional techniques only. According to “Notice to marketing authorisation holders, Part II B Method of preparation” a validation for the preparation of the Solution is not required. The critical process parameters have been validated. The sterilisation of empty vials, stoppers and filled vials was presented. The steam autoclave and the dry heat steriliser have been validated.

CONTROL OF STARTING MATERIALS

Active substance

The active substance meloxicam is listed in the British Pharmacopoeia The active ingredient is the same as previously approved for Metacam 5 mg/ml solution for injection for cattle.

Specification and routine testing

The specifications and routine tests were presented. The used methods are validated and the method for assay of meloxicam was shown to be selective with good linearity and repeatability. Results from 6 batches showed satisfactory agreement. For determination of robustness, repeatability and reproducibility were made. Reference was made to certificate of analysis of three batches, tested by two different production sites. The results obtained were comparable.

Batch results and justification of the specification

Batches manufactured for clinical study and normal production show analytical data of purity testing at a level considerably lower than the specification limits and below the current quantification limits.

Reporting format for particle size measurements is not uniform. The particle size distribution is not critical for the present formulation and should be judged when suitability for solid formulations is assessed.

Process validation and in process controls

The process is monitored for reaction completeness by TLC. In the quality control of starting materials, the relevant purity testing and limitation of structurally related substances is shown.

Other ingredients

Each batch of excipient is analysed in accordance with respective pharmacopoeia.

Excipients listed in a pharmacopoeia

All the inactive ingredients, with the exception of a solvent, conform with relevant pharmacopoeial monographs.

Excipients not listed in a pharmacopoeia

Adequate general and specific tests are performed for the solvent and the limits applied, including not more than 1 ppm of ethylene oxide, are acceptable.

CONTROL TESTS OF THE FINISHED PRODUCT

Specification and routine testing

The quality of the finished product at release and throughout its shelf life is assured by the proposed analytical procedures and limits.

Validation

The validation of analytical methods was presented. The method used for simultaneous determination of decomposition and assay has been satisfactorily validated for selectivity, linearity, accuracy and precision. Acceptable validation data in support of the method for determination of ethanol content in respect of linearity, accuracy, selectivity and precision have been presented.

Batch analysis

Results of batch analysis were presented. Three batches, size 1025 litres, have been submitted. All results were within the stated specifications.

STABILITY

Stability studies on the active substance

Two stability reports have been presented. Both studies are the same as have been presented earlier for Metacam 5 mg/ml solution for injection for cattle with addition of complementary data for the second

study that was ongoing at that time. The marketing authorisation holder has provided additional data, now covering up to 36 months at 25°C/60 %RH and at 30°C/70 %RH for 3 batches packed in polyethylene bags in fibre drum.

One additional batch has also been stored at 40°C/75% for up to six months and two batches have been re-stored for up to 6 months at 40°C/75%.

Subsequently, stability data from 60 months storage has been presented. . The proposed re-test period of 60 months is acceptable.

Stability tests on the finished product

Stability tests on the finished product were presented. Stability data from storage up to 36 months of two batches manufactured in variable scale and with a nominal filling volume of 10 ml are presented. Supplementary stability test results are available from three additional batches. In addition one batch with a nominal filling volume of 50 ml was included. The batches have been stored for up to 36 months in upright and horizontal position respectively. One batch is manufactured with a different quality of stopper. Storage conditions are 25°C/60 %RH (36 months data), 30°C/70 %RH (12 months data) and 40°C/ambient RH (6 months data). Parameters studied are appearance, odour, colour, pH, content of ethanol, content of meloxicam, decomposition and sterility. The marketing authorisation holder has given satisfactory explanations about the composition and the possible influence of the different ingredients on the product stability. The influence of low temperatures and of light has been presented.

On the basis of the results from up to 36 months storage, a shelf-life of 3 years stored below 25°C, can be accepted for Metacam 5 mg/ml solution for injection for dogs and cats.

In-use stability

Two batches of 10 ml vials and another batch were examined for in-use stability. The first study was performed with a batch recently manufactured when the study was initiated and samples were extracted during a 6 months period. Samples from the two other batches were extracted during a 4 week period. The increase in decomposition estimated or observed during the proposed in-use time of one month was acceptably low. The solution from in-use test samples was later tested and found to have preservative effectiveness according to Ph. Eur. An in-use shelf-life of four weeks is acceptable.

SAFETY ASSESSMENT

Two studies involving the target species dog using an acute intra-articular inflammation model were presented.

Pharmacokinetics

A pilot study was performed in one male and one female mini-pig. Both animals were given 3.5 mg/kg of ^{14}C-labelled meloxicam orally. The distribution of total radioactivity was studied after 4 hours. High radioactivity was found in kidney and liver. Low activity occurred in the brain, indicating the existence of a blood/brain barrier for meloxicam. The plasma/tissue ratios were high, indicating a low volume of distribution of the drug or its metabolites.

The parent compound dominated in plasma. The reverse situation occurred in urine and bile, where the contribution to the total radioactivity by the parent compound was less than 3%. The major metabolites, an acid and an alcohol, were identified in earlier studies. The in vivo protein binding was about 96%.

The total recovery of radioactivity after analysis of tissues and excreta was 82% in the male and 71% in the female. Considerable radioactivity was found in urine (17-31%) and in faeces (2-9%).

Biliary elimination proceeded in a continuous manner. About 60% of the dose was eliminated in faeces during 96 hours after treatment. Faecal excretion was not completed by this point, and was calculated to proceed for a further 2 days. Renal elimination accounted for about 25% of the administered dose and was largely completed after 96 hours.

The pharmacokinetics and bioavailability of meloxicam after i.v., oral and s.c. administration were studied in beagle dogs. The study was of cross-over design. Each dog received 0.2 mg of meloxicam as a single dose 30 min after a standard meal of pelleted feed and meat. The wash-out period was 2 weeks.

The mean elimination half-life was similar after all routes of administration, about 24 h with a range from 17 to 36 h. No major differences were observed for the other parameters, except for C_{max} and T_{max} after oral and s.c. administration. C_{max} was 0.464 $\pm$ 0.059 µg/ml after oral administration and 0.734 $\pm$ 0.117 µg/ml after s.c. injection. The corresponding figures for T_{max} were 7.5 h and 2.5 h. Plasma protein binding was 97%.

The bioavailability after both oral and s.c. administration is 100%. The metabolite profiles in bile and urine are in line with earlier results obtained in other species and the elimination takes place largely via the bile. Plasma protein binding was high which should be borne in mind as regards possible interactions. This item is adequately covered in the SPC.

The pharmacodynamic properties of meloxicam have been evaluated in laboratory species, cattle and dogs. One study documenting pharmacokinetics after single dose administration in cats was also submitted.

Eight adult cats, 4 males and 4 females were randomly allocated to two groups. The animals were treated i.v., s.c. and p.o. with Metacam at the dose 0.3 mg/kg b.w. The study was of cross-over design and the wash out period between treatments was 14 days. Metacam 5 mg/ml solution for injection was used for the i.v. and s.c. administration and Metacam 1.5 mg/ml suspension was used for the oral administration. Blood samples were collected prior to and 0.5, 1, 3, 6, 10, 24, 48, 72 and 120 hours after treatment.

Meloxicam in plasma was analysed using reversed phase HPLC separation and UV detection. The method was previously fully validated for human plasma over the concentration range 0.05 µg/ml to 2.5 µg/ml and was revalidated for cat plasma. The limit of detection was 0.05 µg/ml. The inter-assay precision was determined as the relative standard variation for spiked control samples. The following values were obtained: 1.9% for 0.2 µg/ml, 2.3% for 0.8 µg/ml and 2.2% for 2.0 µg/ml. Accuracy, determined as the deviation from the theoretical value was 1.5%, 0.8% and 2.2% for the spiked samples. The absolute oral and subcutaneous bioavailability was examined in a two-way cross-over trial in parallel for i.v./s.c. and i.v./p.o. administration.

The pharmacokinetic parameters were determined using non-compartment methods of a commercially available program (TopFit) and are summarised in the table below:

	Group 1		Group 2	
Parameter	**i.v. ± SD**	**p.o. ± SD**	**i.v. ± SD**	**s.c. ± SD**
$t_{1/2}$	16.8 4.93	15.6 5.04	14.6 3.96	14.5 3.56
AUC µgh/ml	26.1 7.84	21.0 7.98	24.0 5.72	24.9 7.73
MRT h	23.7 6.77	22.4 7.13	20.3 5.94	21.1 5.67
Cl ml/min	0.2 0.07	0.3 0.16	0.2 0.05	0.2 0.05
V_d l	0.3 0.02	0.3 0-06	0.3 0.01	0.3 0.03
C_{max} µg/ml		0.9 0.16		1.1 0.05
T_{max} h		1.5 0.87		1.5 0.87

The means of the pharmacokinetic parameters were similar after all routes of administration. However, there were individual variations, e.g. the half-life after oral dosing varied from 9 to 22 hours. The bioavailability after oral administration was 80% and after s.c. administration 100%. Protein binding in cat plasma was determined by ultrafiltration and was found to be 97.6%.

A preliminary simulation of plasma concentration-time profiles was performed in two cats for an oral loading dose of 0.3 mg/kg b.w. followed by oral doses of 0.1 mg/kg b.w. with 24 hours interval. Steady-state was reached after 2-3 days with peak plasma values of 0.5 and 0.6 µg/ml and trough values of 0.15 and 0.3 µg/ml.

User Safety

No adverse effects at the injection sites were noted in any of the dose groups. There was no evidence of a sensitisation reaction. Similarly, no sensitisation reaction was reported with placebo gel, but a positive reaction was found with a 0.3% DNCB formulation. No potential for ocular irritation was noted with a formulation including meloxicam at a concentration of 0.5% was found. The formulation tested differed however in the content of excipients from the applied formulations and some of the excipients were not included.

There were no remarkable findings regarding clinical signs, changes in body weight, haematology, clinical chemistry, and urinalysis. There were also no reported adverse effects revealed at (thorough) autopsy, including a lack of findings at the site of application. Thus, it appears that meloxicam in topical solution was without local as well as systemic effects in this study. The dermal absorption of meloxicam was 5-30% of that absorbed orally. Whilst the composition of the formulation tested for dermal irritation was not identical to the applied oral formulation. It is, however, considered unlikely that the other excipients contained in Metacam oral suspension would cause dermal irritation in the volumes used in clinical practice.

In an open, two-way cross-over, randomised clinical trial the bioavailability and tolerability of meloxicam in a single subcutaneous dose of 15 mg was evaluated in comparison with intravenous administration of an equal dose. Almost all subjects experienced a burning feeling at the injection site in a mild to moderate degree lasting up to 43 minutes after injection. The bioavailability of meloxicam was 100% after subcutaneous injection.

In a further open, two-way cross-over, randomised clinical trial, male volunteers received seven daily doses of 15 mg meloxicam either as syrup (7.5 mg/ml) or in capsules. The relative bioavailability of the two dosage forms was estimated at steady state. Tests of myocardial functions, urinalysis, haematology and plasma biochemistry were performed.

In rabbits, meloxicam showed no potential for causing dermal irritation after topical administration in a gel formulation for 28 days in a dose of 5 mg/rabbit, with a maximum estimated absorption of 30%. There was no evidence of a sensitisation reaction in guinea pigs of a gel formulation containing 1% meloxicam. There was no potential for ocular irritation of meloxicam administered as an eye drop formulation, not identical to the applied formulations, in doses up to 0.5%.

Intramuscular injection of the formulation of meloxicam for human use in healthy volunteers and rabbits was therefore regarded as well tolerated. The tolerability of the formulation of meloxicam for human use was also good after intravenous and subcutaneous administration. The warning previously included in the SPC for Metacam 5 mg/ml solution for injection for cattle that accidental injection may give rise to pain has also been included in the SPC. The warning concerning individuals sensitive to NSAIDs has also been included in the SPC.

CLINICAL ASSESSMENT
Tolerance in the target species (Dogs)

The tissue reactions after a single subcutaneous injection were studied in rats. Slight haemorrhages, cell infiltration and necrosis occurred in all animals in the placebo and Metacam groups after 24h. The conclusion of the study was that the Metacam injectable formulation was well tolerated.

The tolerance after i.v., i.m., and s.c. injection and after dermal, rectal, and eye-drop application of a Meloxicam formulation was studied in laboratory animals (rats, guinea pigs and rabbits). The total composition of the formulation is not given, but it is stated that the formulation was the one intended for human use.

An in vitro haemolysis test was also performed, where Metacam was compared with a number of earlier authorised NSAIDs. The test was performed with human blood. The degree of haemolysis induced by the undiluted Metacam formulation was < 2%. All other tested NSAIDs (piroxicam, ketoprofen, indomethacin, diclofenac and ibuprofen) induced > 10% haemolysis.

A full autopsy was performed of animals killed on days 2, 5 and 7. Subcutaneous injection of Metacam to rabbits resulted in minor macroscopic and microscopic changes. Reddening of the musculature, small focal haemorrhages in subcutis and necrosis of single myofibres were the most prominent findings. Similar changes were found in the control group injected with physiological saline. Similar findings were obtained also after i.m. injection of Metacam. Slight focal skin epithelial necrosis and focal necrosis of muscle fibres were found. S-CK was measured before treatment and at the time of sacrifice. It is stated that no increases occurred, but the mean or individual values for the enzyme activity were not given. There were no ocular changes indicative of poor ocular tolerance after 4 weeks of treatment (50 µl, doses up to 0.3 % meloxicam).

Metacam also appeared to be well tolerated after dermal and rectal application. The animals were treated daily for 4 weeks. No drug-related histological changes were found in the skin or anus. The composition of the gel used for dermal application and the suppositories is not given. It was stated that the formulations were the ones intended for human use.

The local tolerance of Metacam solution for injection and an injection solution of ketoprofen (10 mg/ml) was compared in healthy dogs. The study was conducted as an open cross-over experiment on two consecutive days. Both test solutions were given at the recommended dose levels, 0.2 mg/kg of meloxicam and 2 mg/kg of ketoprofen. Eight dogs with body weights ranging from 11.9 kg to 35 kg were included in the study. The injected volumes of Metacam varied from 0.63 to 1.06 ml and the volumes of ketoprofen from 2.4 to 7 ml. Pain reactions at the time of injection were carefully monitored and the injection sites were inspected for inflammatory reactions after 24 hours. Both formulations were well tolerated, slight pain reactions occurred in single dogs in both groups. No inflammatory reactions were found in any of the dogs.

A study, submitted as part of an inaugural dissertation from the School of Veterinary Medicine at the University of Giessen, was presented. The tolerance of 0.2 mg/kg b.w. of meloxicam given as a daily

oral dose for 4 weeks was studied in healthy Beagles. The age of the dogs used in the study varied from 1.5 to 13 years. Slight fluctuations in appetite and changes in faecal consistency were observed in some dogs after the dose 0.2 mg/kg/day. Occult blood was detected in faeces and persisted for 1-3 days in all dogs except two. The higher dose, 0.3 mg/kg/day appeared to cause more severe gastro-intestinal symptoms. The appearance of occult blood in faeces persisted longer than after the lower dose. Several dogs of group B showed haemorrhagic gastro-enteritis at the end of the study. The test for parvovirus was positive which made the interpretation of the results more difficult.

Whilst no certain conclusion can be drawn, the results indicate that meloxicam may induce symptoms from the gastro-intestinal tract. No clinical signs occurred during the treatment period. Both test kits for blood in faeces showed positive results for individual animals from week 2 until sacrifice, but no relevant differences between the control group and the treated groups occurred. The authors concluded that the value of the test could be questioned, as there were no signs of gastrointestinal lesions at autopsy. No macroscopical or microscopical lesions were found in the kidneys or in other organs. No treatment related changes were found in any of the studied clinical chemistry parameters.

Beagles, aged 6-8 months, were included in a target animal tolerance study. The body weights varied from 6.95 kg to 9.85 kg. The dogs were allocated to 4 groups and given a single subcutaneous injection of Metacam and were thereafter treated orally with the Metacam oral suspension for the following 6 days. The subcutaneous doses were 0, 0.2 mg/kg, 0.4 mg/kg, and 0.6 mg/kg. The oral dose was 0.1 mg/kg. The animals were treated about 30 min. after the morning feeding. Clinical signs, body weights, food and water consumption were recorded. All dogs were autopsied after a recovery period of 7 days.

No clinical signs occurred and body weights, food and water consumption remained unaffected. Faeces were tested for the presence of occult blood. A positive result was seen in one female of the control group on day 4, and in one male of the intermediate dose group on day 5. All other samples were negative. All changes were considered to be consistent with the expected background pattern of observations in dogs of this breed and age. No consistent changes that could be related to treatment occurred in the studied haematological and clinical chemistry parameters.

Dogs are known to be very sensitive to the ulcerogenic effect of NSAIDs. The presence of blood in faeces was carefully tested and only two positive samples were found, one of the samples was found in the placebo group. No signs of ulceration or haemorrhages in the gastro-intestinal tract were found at necropsy. Thus, the treatment appeared to be well tolerated.

Transient gastro-intestinal symptoms, e.g. vomiting, soft stool and diarrhoea occurred in dogs in a further study during the acclimation period before treatment as well as after treatment. However, the authors found it difficult to relate the symptoms to treatment, since transient symptoms occurred also during the wash-out periods. The general impression was that meloxicam was well tolerated.

Periodic Safety Update Report (1993 – 1998)

Metacam solution for injection and oral suspension are approved in a number of Member States and also in countries outside EU. The marketing authorisation holder has submitted a Periodic Safety Update Report covering the period February 1993 to September 1998. February 1993 was the time Metacam was first launched. Up to 1996, the report is based only on Metacam oral suspension. From 1999 onwards, both formulations are covered.

According to the original recommendation, a dose of 0.2 mg/kg should be given during the first week of treatment, thereafter the dose should be decreased to 0.1 mg/kg. A risk assessment to further improve the risk/benefit ratio was performed by BgVV in Germany. The present dose recommendation, 0.2 mg/kg the first day and thereafter 0.1 mg/kg/day, was approved in Germany in 1995, and later in most other countries.

An overview of the sales volume in different countries is provided, and based on these data and the number of adverse reaction reports, the incidence of adverse reactions could be calculated. The

marketing authorisation holder has taken a conservative approach in the calculations to overcome the difficulties caused by the changed posology. A dosage of 0.2 mg/kg was assumed for all treatments, and the mean body weight of the treated dogs was set to 30 kg, based on the mean weights of the dogs in the clinical studies. Based on these figures, the daily dose of meloxicam will be 6.0 mg.

The total number of doses sold correspond with an average number of approximately 15 000 dogs treated each day during the period of 6 years. The figures for the number of doses sold and the number of dogs treated is obviously underestimated, when the changed posology is taken into consideration.

The distribution of the suspected ADRs to the different Member States, the ADRs with fatal outcome and the incidence of these events were also provided.

The number of cases with a fatal outcome has remained at a rather constant level despite an increased usage of the product. The decrease in the incidence of cases with fatal outcome is probably the result of the reduced dosage.

The distribution of SADRs in different symptomatic groups was also presented. As expected for this class of compounds, the gastrointestinal symptoms dominated. The most common gastrointestinal signs were vomiting and diarrhoea with and without blood, and ulceration. The incidence of renal symptoms was unexpectedly low. A large number of the dogs in this group were old, more than 10 years of age and pre-existing renal disorders were diagnosed in some cases.

One case of adverse reaction in humans was reported. An adult woman developed dermal inflammation and blistering after contact with Metacam oral suspension. The lesions were mild and healed spontaneously.

The Periodic Safety Update Report was well and concisely written and the data presented appear to be properly interpreted. Gastrointestinal and renal adverse reactions could be expected of compounds like Metacam. The number of cases with central nervous symptoms was unexpected, and it cannot be excluded that these signs were treatment related. However, Metacam can be considered as safe for dogs under field conditions.

One human case was reported after dermal contact with the oral suspension. As the product was well tolerated after eye-drop and dermal application, this case may be an allergic reaction.

Conclusions on tolerance in the target species (Dogs)

The local tolerance after parenteral administration was studied in laboratory animals and in the target species. Subcutaneous Injection of Metacam Solution for Injection to rabbits resulted in minor macroscopic and microscopic changes. Reddening of the musculature, small focal haemorrhages in subcutis and necrosis of single myofibres were the most prominent findings. Similar changes were found in the control group injected with physiological saline.

Similar findings were obtained also after i.m. injection of Metacam. Slight focal skin epithelial necrosis and focal necrosis of muscle fibres were found. Metacam Solution for Injection was well tolerated in dogs except for slight pain reactions in single individuals. No inflammatory reactions were noted.

Dogs are known to be very sensitive to the ulcerogenic effect of NSAIDs. The Periodic Safety Update Report gives a good view on the pattern of adverse reactions including fatalities, while the results of the safety studies were largely negative. Single cases of blood in faeces occurred, but no lesions were found in the gastro-intestinal tract.

Reference to the occasional side-effects, in rare cases serious or fatal, has been mentioned in the SPC. It is acknowledged that the change in the dosing regime from 0.2 mg/kg during the first week of treatment to 0.2 mg/ during the first day of treatment probably is associated with the decrease in the incidence of cases with fatal outcome over the years of marketing.

Safety was not documented in pregnant and lactating females and a relevant warning for use in pregnant and lactating bitches was included in the SPC. As safety was not documented in puppies and very few young dogs were included in the safety studies Metacam is contraindicated in dogs less than 6 weeks of age.

Tolerance in the target species of animal (Cats)

A) Local tolerance

The local tolerance of Metacam 5 mg/ml solution has been extensively studied in laboratory animals and in dogs. The studies were included in the original application. Subcutaneous injection in rabbits caused minor macroscopic and microscopic changes similar to those caused by injection of physiological saline. Reddening of the musculature, small focal haemorrhages in subcutis and necrosis of single myofibres were the most prominent findings. The product was well tolerated in dogs with slight pain reactions observed in single individuals. Good local tolerance in cats was reported in the GLP compliant target animal safety study.

B) Systemic tolerance

Four separate cat tolerance studies were submitted.

1. Tolerance study in cats on meloxicam (Metacam) at dose levels of 0.3 and 0.6 mg/kg body weight given as single subcutaneous injections followed by oral treatment of the same dosages for 9 consecutive days

Twelve adult cats, six males and six females, were randomly allocated to three equal groups. Group 1 received a single s.c. injection of placebo on day 0, followed by daily oral placebo dosing for 8 days. Groups 2 and 3 were given s.c. injections of 0.3 and 0.6 mg/kg b.w., respectively, on day 0 followed by oral administration of the same doses for 8 days.

The study was originally designed for a treatment period of 10 days, but 2 cats, one in group 2 and one in group 3, were found dead on day 8. These animals had shown depressed demeanour and reduced appetite since days 3-4 of the study. After 8 days of treatment depressed demeanour and gastrointestinal signs occurred in two cats in group 2 and in three cats in group 3. On day 9 all meloxicam treated animals showed clinical signs (animal more subdued than normal), the study was terminated and all surviving animals were necropsied. Pyloric/duodenal ulceration and peritonitis were found in two cats of the highest dose group. Signs of peritonitis were found also in the other two cats of this group, but the pylorus/pyloric duodenal junction was not investigated histologically in these animals. Minimal signs of peritonitis occurred also in two animals treated with 0.3 mg/kg b.w. over 8 to 9 days. Granulomatous inflammation of the intestinal wall was found in one animal. Feline Infectious Peritonitis was excluded by serological investigation.

Clinical signs of NSAID toxicity were a depressed demeanour and gastrointestinal signs. Pathohistological pyloric/duodenal ulceration and peritonitis were described. No treatment related haematological or blood chemical changes were found. Faeces was tested for the presence of occult blood during the study, and positive samples were found in all groups (including placebo) at all time points and also pretreatment. Similar experiences were recorded in earlier dog studies, and the conclusion was drawn that commercial kits for the testing of blood in faeces are not reliable. The findings of the study were that repeated administration of meloxicam at the doses 0.3 and 0.6 mg/kg b.w. followed by oral administration of the same doses for 8 days can cause pyloric and duodenal ulceration and that the risk/benefit needed to be evaluated at lower dose levels.

2. Tolerance study in cats on meloxicam (Metacam) at dose levels of 0.3 and 0.6 mg/kg body weight given as single subcutaneous injections followed by oral treatment at reduced dosages for 9 consecutive days.

This study was performed according to a similar protocol as study VU-00220 with the only difference being a reduction of the doses administered. Twelve cats of both sexes were allocated to three equal groups. Group 1 was treated s.c. with placebo on day 0 and thereafter with daily oral placebo doses for 9 days. Group 2 received a s.c. injection of 0.3 mg/kg b.w. followed by 9 daily oral doses of 0.1 mg/kg b.w. Group 3 was treated s.c. with 0.6 mg/kg b.w. followed by 9 daily oral doses of 0.2 mg/kg b.w.

The only clinical sign of NSAID toxicity was a depressed demeanour in sensitive animals. Inflammation of the gastrointestinal mucosa was the predominant pathological finding in the majority of treated animals. Beside that a case with inflammatory signs of the duodenal mucosa and a single case of duodenal ulceration and secondary peritonitis were described. Metacam treatment did not induce any consistent changes in haematological or blood chemical parameters. The results confirmed the sensitivity of cats to NSAIDs and that the therapeutic index for Metacam is narrow.

3. Clinical efficacy and tolerance of two parenteral meloxicam (Metacam) formulations given as a single subcutaneous injection followed by subsequent oral treatment of meloxicam (Metacam) in cats with acute locomotor disorders.

Cats suffering from locomotor disturbances of varying etiology were included in the study. The animals were treated s.c. with a loading dose of 0.3 mg/kg b.w. followed by 0.1 mg/kg b.w. orally for 4 days. Two different injection formulations of Metacam were used, the multi-dose vial applied for and single dose ampules. The only difference between the formulations was the presence of a preservative (ethanol) in the multi-dose-vial. Metacam suspension 1.5 mg/ml was used for the oral treatment.

A total of 75 cats were recruited to the trial, 71 animals were available for the final evaluation. The age of the animals varied from 4 months to 17 years. A number of clinical parameters (general demeanour, food intake, degree of motionless weight bearing, mobility, signs of local inflammation and pain on palpation) were scored before and after treatment.

No general or systemic adverse reactions occurred. Transient pain reaction at the time of injection was observed in two cats. It was emphasised that no blood chemical investigations were performed. Metacam can be nephrotoxic and clinical signs appear very late in this pathological process. It would have been more informative if the study had included the monitoring of the blood levels of urea and creatinine, however no haematological or blood chemical changes occurred in the tolerance studies where higher doses were used for a longer period of time.

4. Metacam 0.5% solution for injection target animal safety study in cats following subcutaneous administration over three days.

Twenty-four cats, 12 males and 12 females, were randomly allocated to 4 groups and treated with placebo and Metacam s.c. for three days. The following doses were used: Group 1 - placebo, Group 2 - 0.3 mg/kg b.w., Group 3 - 0.9 mg/kg b.w. and Group 4 - 1.5 mg/kg b.w.

The animals were observed daily for clinical signs. Body weight and rectal temperature were determined at intervals and food and water consumption were recorded daily. Blood and urine samples were collected for laboratory investigation. Faeces were collected for determination of occult blood. All animals were necropsied at the end of the study. No treatment related clinical symptoms were observed and treatment did not influence food and water consumption. No relevant effects on the mean values of haematology, biochemical or bone marrow parameters were found. Alkaline phosphatase was significantly lower in groups 2 and 3 on day 4, and creatinine was significantly lower in groups 2 and 3 on day 4.

There was no significant effect on treatment on urinalysis parameters. Blood in faeces was found in several animals including the controls. Five out of 6 cats in groups 4 (1.5 mg/kg) showed papillary necrosis of the kidney. Mucosal erosions in the jejunum occurred in one cat receiving 0.9 mg/kg b.w. and in 2 cats at 1.5 mg/kg.

No treatment related changes were found in the animals treated with 0.3 mg/kg b.w. and good local tolerance was reported.

The results of the tolerance studies confirm that cats are more sensitive to NSAID side effects than other species. An s.c. loading dose of 0.3 mg meloxicam/kg b.w. or more followed by daily oral doses of 0.1 mg/kg b.w. or more for 9 consecutive days can induce significant gastrointestinal adverse reactions. Good local tolerance was shown in the target species.

No adverse reactions occurred in the combined safety and efficacy study where the animals were given a loading dose of 0.3 mg/kg b.w. followed by daily oral doses of 0.1 mg/kg for 4 days.

The recommended posology of 0.3 mg meloxicam/kg b.w. given as a single s.c. treatment was shown to be safe but follow-up with oral administration cannot be tolerated and cannot, therefore, be recommended.

Clinical studies

DOGS

Clinical efficacy and tolerance of Metacam for long-term treatment of chronic canine locomotor disorders

Sixty-two dogs with chronic locomotor disorders were recruited and randomly allocated to two treatment groups. Group A was given an oral meloxicam dose of 0.2 mg/kg b.w. for a period of 21 days, thereafter the dose was reduced by 50%. Group B was given 0.2 mg/kg for 7 days followed by a 50% dose reduction. The treatment period was 3 months in both groups.

Clinical examination was performed on day 1, day 7, day 21 and after 3 months. A general and a more specific locomotor examination was performed at each occasion.

Blood samples for routine haematological and clinical chemistry investigation were collected before treatment, after 3 weeks and after 3 months.

The localisation of the disorders were hips, stifle and elbow joints. Forty-five of the 62 recruited cases were available for evaluation, 23 in group A and 22 in group B.

The mean scores for the specific locomotor parameters improved in a similar way in the two groups from the first to the last clinical examination. No differences between the groups could be seen. The mean mobility score, representing the sum of the locomotor parameters, was calculated for each group. Both groups improved significantly, but no differences between the groups occurred. Eleven cases of adverse reactions were observed, 6 in group A and 5 in group B. Most cases occurred during the first 8 days of treatment. Vomiting was the dominating symptom (5 cases). Other symptoms were diarrhoea, polydipsia, ataxia and dermatitis. All cases were rather mild and specific treatment was not required. The symptoms disappeared during the course of treatment.

The mean values of the haematological parameters prior to therapy were similar for both groups. Minor changes occurred during the course of therapy, but the changes were not consistent and did not deviate from the physiological range.

The conclusion of the study was that the used doses of meloxicam was safe and effective for the long-term treatment of locomotor disorders in dogs, and further that the initial dose of 0.2 mg/kg b.w. may be reduced by 50% after 7 days.

Clinical efficacy and tolerance of a parenteral and oral treatment with Metacam over 5 consecutive days in comparison to a similar treatment with ketoprofen in dogs with acute locomotor disorders.

The aim of the study was to compare the clinical efficacy and tolerance of meloxicam and ketoprofen in the treatment of acute locomotor disorders in dogs.

The animals were randomly allocated to two treatment groups. One group was treated with a single subcutaneous injection of Metacam at the dose 0.2 mg/kg b.w. followed by daily oral treatment with Metacam suspension at the same dose level for 4 days. The other group was given 2 mg/kg b.w. of ketoprofen subcutaneously on day 1 followed by 1 mg/kg b.w. orally for the following four days.

The dogs were studied for 12 days. A total of 104 dogs were originally recruited, of which 95 became available for evaluation, 47 in the Metacam group and 48 in the ketoprofen group. Before treatment, a disturbed general demeanour was observed in 15 dogs (32%) of the Metacam group and in 18 dogs (37%) of the ketoprofen group. A continuous and similar improvement was observed in both groups after initiation of therapy. At the examination on day 6, all Metacam treated dogs and 45 of the 48 dogs in the ketoprofen group showed a normal general demeanour. The difference between the groups was not significant.

The specific locomotor parameters were evaluated during each clinical examination. There were no significant differences between the mean scores for motionless weight-bearing, locomotion, local inflammation and palpatory pain under the course of therapy. However, a mean mobility score representing the sum of all 4 locomotor parameters was calculated for each dog. A significant difference between the group means in favour of Metacam was observed on days 2 and 6. On day 6,the overall clinical efficacy was judged as excellent/good in 98% of the cases in the Metacam group and in 90% of the cases in the Ketoprofen group.

Clinical examination on day 12 revealed 1 relapse case in the Metacam group and 3 in the ketoprofen group. Both treatment regimes were well tolerated, no local reactions were observed after the subcutaneous injection. One case of vomiting was observed in the ketoprofen group and one dog in this group showed severe haematuria.

The suggested dose of meloxicam, 0.2 mg/kg on the first day and 0.1 mg/kg/day for the rest of the treatment course, was not used in the studies. Therefore, the studies do not support the suggested dose. However, the studies give a good picture of the pattern of adverse reactions. In general, the adverse reactions were rather mild and no specific treatment was required.

Clinical efficacy and tolerance of two parenteral meloxicam (Metacam) formulations given as single s.c. injections followed by subsequent oral treatment with meloxicam (Metacam) in dogs with acute locomotor disorders.

The aim of this trial was to study safety and efficacy in dogs with acute locomotor disorders.

The dogs were randomly allocated to two treatment groups. After a thorough clinical examination, all dogs were given a subcutaneous injection of meloxicam at the dose 0.2 mg/kg followed by oral treatment with the same dose for up to one week. The only difference between the groups was that a multidose vial of the injection formulation was used in group A, while 1 ml ampoules were used in group B. Some special parameters for defining the locomotor disorder were scored.

Thirty-one dogs in each group were evaluated. The most common diagnoses were contusions/sprain caused by trauma and acute arthrosis or arthritis.

The mean scores for the specific locomotor parameters under the course of therapy were provided. The score mean for all parameters were significantly lower on day 6 than on day 1. The overall clinical response was judged as Excellent/Good in 96% of the dogs in group A and in 90.8% in group B on

day 6. The adverse reactions were few, a single case of vomiting and one case of diarrhoea were observed in group B. One dog in group A showed transient vomiting and diarrhoea. Additional therapy was not considered necessary and the medication with Meloxicam was not discontinued.

The suggested dosage was not used in this uncontrolled study. Both groups were treated in the same way, and as expected both groups responded similarly. However, the results are adequately described and discussed.

Placebo-controlled study on clinical efficacy and tolerance of a single subcutaneous injection of meloxicam (Metacam) followed by oral treatment over 6 consecutive days in acute canine locomotor disorders.

A blinded and placebo-controlled study was performed at four different centres in Germany. A total of 89 dogs were recruited to the study. The dogs were randomly allocated to two treatment groups. One group was given a subcutaneous injection of 0.2 mg/kg on the first day of treatment, the other group was given placebo. Thereafter, all dogs in both groups were treated orally with 0.2 mg/kg for the following 6 consecutive days.

Forty-six dogs in the full treatment group and 41 in the placebo/meloxicam group were available for evaluation. A total of 8 dogs less than one year old were included. The dominating diagnosis was arthropathies.

The special locomotor parameters were scored. Clinical examination was performed before inclusion and then on days 1, 2 and 8. The scores for the studied parameters on the selected time points were provided. Improvement was achieved of all the studied parameters within both groups. A statistical comparison was made between the groups and a small but significant difference ($p< 0.05$) occurred between the scores for motionless weight-bearing, locomotion and local inflammation on day 8.

The differences between the groups were not statistically significant, but were seen as a confirmation of the results obtained for the special locomotor parameters. Eleven cases of adverse reactions were observed. Gastro-intestinal signs, vomiting and diarrhoea, occurred in 4 dogs. The signs were considered as mild and transient. Other observed signs were polydipsia and polyphagia. Special treatments of the adverse reactions were not considered necessary. Additional therapy was given to 7 dogs by one investigator. However, the additional treatment was given for skin disorders, hormonal deficiencies and cardiovascular diseases and were not considered to be relevant for the clinical evaluation.

The difference in clinical response in the two groups was small, but statistically significant for some locomotor parameters. The difference was most evident after 8 days. It was considered rather unlikely that one additional treatment compared with the control group was the only explanation. Very early treatment under the supervision of a veterinarian was considered to be the most probable explanation of the difference in response between the groups.

Clinical efficacy and tolerance of a reduced dose level for meloxicam (single dose of 0.2 mg/kg followed by 0.1 mg/kg once daily) versus the established once-daily dose of 0.2 mg/kg for 7 days of treatment in dogs with acute locomotor disorders.

The aim of the study was to compare the clinical efficacy and tolerance of 3 different meloxicam treatment schedules in dogs suffering from acute locomotor disorders in order to investigate the therapeutic implications of an early dose reduction from 0.2 mg/kg to 0.1 mg/kg from the second day of treatment.

Clinical cases of acute locomotor disorders were recruited to the study. The dogs were randomly allocated to 3 different treatment groups:

Group A Once daily oral administration of 0.2 mg meloxicam/kg b.w. for 7 days (69 dogs)

Group B A single oral administration of 0.2 mg meloxicam/kg b.w. on day 1 followed by 6 daily oral doses of 0.1 mg/kg (66 dogs).

Group C A single subcutaneous injection of 0.2 mg meloxicam/kg b.w. on day 1 followed by 6 daily oral doses of 0.1 mg/kg (64 dogs).

Clinical examination was performed before inclusion and on days 2 and 8. The locomotor disorder was defined by scoring systems. The mean scores for mobility, local inflammation and palpatory pain were comparable in each group on day 1 and were reduced at each clinical examination. The lowest scores were obtained on day 8. No differences could be found between the groups. More than 90% of the dogs in each group showed undisturbed demeanour on day 8. Evaluation of the overall clinical efficacy showed that treatment groups A, B and C produced excellent/good scores of 88.4%, 87.9% and 95.3% respectively.

No adverse reactions could be observed after subcutaneous injection in group C. Four cases of vomiting and diarrhoea occurred in group A, the symptoms were not severe and were characterised as single events. One case occurred in group B. The dose was reduced in order to reduce the risk of adverse reactions. The number of treated dogs is sufficient for valid conclusions. The results showed that the dose could be reduced without loss of therapeutic activity.

Clinical efficacy and tolerance of Metacam (meloxicam) during a 28-day oral treatment period in dogs suffering from chronic locomotor disorders.

The study was performed at 6 different centres in France. Fifty-seven dogs suffering from chronic locomotor disorders were originally recruited to the study and 50 were available for the final evaluation. The trial was conducted as a randomised placebo controlled multi-centre study. The dogs were allocated to two treatment groups: Metacam (group A) and placebo (group B).

A clinical assessment was made for each dog. Metacam or placebo product was administered for a period of 28 days. The dose was 0.2 mg/kg orally on day 1, followed by 0.1 mg/kg orally on the subsequent 27 days. Blood was collected on days 1 and 28 and urea and creatinine were analysed for evaluation of the renal function.

The most frequent diagnoses were arthrosis and arthrosis+dysplasia. The numbers of animals showing improvement in the components of the global score on days 7, 28 and 42 in comparison with the pre-treatment value were presented.

Relapses occurred and the global scores were significantly higher in both groups on day 42. The change in lameness score was significant in both groups. Adverse reactions were reported in both groups. Seven cases of vomiting and diarrhoea occurred in the Metacam group and 8 in the placebo group. Constipation occurred in one dog in the Metacam group and in 3 dogs in the placebo group. Other reported signs were reduced appetite, dysuria, respiratory signs and changed behaviour. Adverse events were reported in 31% of the dogs in the Metacam group and in 44% in the placebo group.

Treatment did not change the blood concentrations of urea and creatinine, indicating that renal function was not impaired. The study was well conducted and reported.

Treatment appeared to be well tolerated and no serious adverse reactions were observed. The number of reported adverse reactions was high in both groups. However, most of the non-gastrointestinal signs were obviously not treatment related. The study was blinded and the assessment of clinical efficacy was based on subjective opinions. The placebo effect was unexpectedly high, 40%. There was a significant difference in global score between the groups, but not in the individual components of the global score, e.g. lameness and stiffness, due to a wide individual variation. The difference between the Metacam and the placebo group was not large, but the results are acceptable when taking into consideration that the dogs had shown symptoms for more than a year.

Clinical evaluation of Metacam suspension; determination of clinical efficacy and tolerance in dogs suffering from chronic locomotor disorders
This study was performed at 7 centres in Canada. Thirty-eight dogs with diagnosed chronic locomotor disorders were randomly allocated to two equal treatment groups. During the first phase of the study, dogs in one group were treated with 0.2 mg/kg of meloxicam on the first day and thereafter with 0.1 mg/kg daily for the following 6 days. The other group was treated with placebo. On day 8, the dogs in the placebo group were given 0.2 mg/kg of meloxicam and thereafter 0.1 mg/kg/day, the medication with 0.1 mg/kg/day continued in the first group. The study was terminated after 28 days.

Body weight, rectal temperature, feed intake, and general demeanour were monitored on days 1, 7, and 28. The special parameters for locomotion were scored independently by the investigating veterinarian and the dog owners on the same days. Body weight, temperature and feed intake remained unchanged during the observation period. The veterinarians and the dog owners came to similar conclusions regarding the scores for the locomotor parameters. There were no differences between the groups on day 1, but the treated group showed significantly lower scores for general stiffness and painful rise on day 28 and also the total scores were lower. On day 28, when one group had been on treatment for 4 weeks and the other group for 3 weeks, there was a significant reduction of the scores for all locomotor parameters. The palatability of the suspension was good.

One dog in the placebo group died during the first phase (unrelated to treatment). Four dogs showed mild gastro-intestinal symptoms (diarrhoea and vomiting). No haematological or blood chemical changes occurred during the treatment period. Metacam oral suspension appeared to be well tolerated and the scores for the locomotor parameters were reduced during the treatment period.

The effects of Meloxicam (Metacam) on Buccal Mucosal Bleeding Time and a Comparison to Ketoprofen and Buthorphanol in Controlling Postoperative Pain in Dogs
The objectives of the study were to evaluate the clinical safety of meloxicam administration with regard to bleeding times, renal, gastric, biochemical or haematological changes.

The study was conducted in two different phases. In phase one, the buccal mucosal bleeding time was evaluated after administration of meloxicam, ketoprofen or placebo. Phase two evaluated the post-operative analgesia, renal, gastro-intestinal and hepatic safety following intravenous administration of the test substances after induction of anaesthesia, but prior to surgery. The surgical procedures were: laparotomy, laparotomy+splenectomy, and laparotomy+cystotomy.

Eighteen dogs were used in phase 1. The buccal mucosal bleeding time was evaluated after administration of a single intravenous dose of the test compounds. Meloxicam was given at a dose of 0.2 mg/kg, and ketoprofen at the dose 2.0 mg/kg. The control animals received only physiological saline. The bleeding time was measured prior to injection, and thereafter at the following time points:
1, 4, 8, 24, and 48 hours post injection. The bleeding time (in seconds) was reported for each individual dog. None of the tested compounds influenced this parameter. The bleeding time is generally considered as an in-vivo test of platelet function.

Phase 2 included 36 dogs which all were pre-medicated with 0.1 mg/kg of acepromazine. An intravenous catheter was placed and anaesthesia was induced with thiopental sodium and maintained with halothane in oxygen. The test compounds, meloxicam, ketoprofen and butorphanol were injected intravenously shortly after induction of anaesthesia. Due to its short duration of activity, butorphanol was administered after completion of surgery to the dogs in the butorphanol group.

Analgesia was evaluated hourly using a Visual Analogue Scale (VAS). Pain was scored from 0 to10. The personnel was experienced in using the VAS. An overall assessment of analgesic response was determined for each dog for the 24-hour post-operative period. The overall evaluation of analgesia gave the following results: Metacam - 8 of the 12 dogs had an overall pain efficacy rating of Excellent, one was rated Good, one was rated Acceptable and 2 were rated Inadequate; Ketoprofen - 8 out of 12 dogs were rated Excellent, one was rated Acceptable and 3 were rated Inadequate; Buthorphanol - one dog was rated Excellent and 11 dogs were rated Inadequate.

The incidence of post-operative vomiting was recorded. Occult blood in faeces was not observed in samples from any of the dogs. Blood pressure and heart rate were recorded during surgery. No consistent differences between the groups were found. Blood was sampled prior to surgery and after 24 and 48 hours for haematological and chemical examination. The packed cell volume (PCV) and total solids (TS) were used as indirect parameters of haemostasis. Both parameters can be expected to decrease if an intra- or post-operative bleeding has occurred. A statistically significant decrease of PCV was observed, but there were no differences between the treatment groups. Also TS decreased, but returned to near normal at 48 hours.

The findings were not considered to be clinically relevant, but as normal responses to surgery. Serum creatinine and urea did not increase significantly above the normal range. There was a tendency for a more pronounced increase in the dogs given butorphanol. Also S-ALT remained within the normal range. A significant increase above the baseline occurred at 24 hours in the ketoprofen group, but the values returned to baseline at 48 hours.

All dogs were autopsied at the end of the study and the macro- and microscopical findings were described in detail. Special attention was given to the kidneys and the gastro-intestinal tract. Healed ulcers were found in two dogs in the meloxicam group, the changes were not considered to be treatment related, but to have occurred prior to surgery. An unexpectedly high number of crypt abscesses in the small intestine was found in single dogs in all groups. Crypt abscesses are defined as dilated crypts containing eosinophilic material and cell debris. This change is seen occasionally in normal dogs, but were abundant in the 3 dogs. However, the changes were considered to be incidental and not treatment related.

CATS
Laboratory trials

1. Pilot study to examine the pyretic response to intravenous endotoxin and the antipyretic potence of meloxicam (0.6 mg/kg body weight) in a feline endotoxin model

The objective of the study was to establish a model for studying the antipyretic potency of meloxicam. The study was performed in two phases. Six adult cats were allocated to two equal groups. In the first phase, one group was injected intravenously with 0.6 mg/kg b.w. of meloxicam followed by 0.5 µg/kg of E. coli endotoxin 30 min later. The other group was treated with placebo and endotoxin. The rectal temperature was recorded every 15 min for 5 hours.

Phase II was performed after 21 days. The only difference from phase I was that the endotoxin concentration was adjusted so that an i.v. bolus of 0.1 ml could be given to each cat. Blood was sampled for haematological examination to confirm the presence of endotoxin. The results were reported for each phase separately, in addition to the combined data.

The placebo groups showed a significant increased body temperature following administration of endotoxin, with peak temperature occurring after 90 min. The mean temperature was 1.7°C lower in the Metacam treated animals. The AUCs of the temperature-time curves differed significantly between the groups. All animals showed the characteristic drop in white blood cell count as a response to endotoxin. The model was found to be suitable for the study of the antipyretic effects of Metacam.

2. Evaluation of the antipyretic potency of meloxicam at 3 different dosages of 0.1, 0.3, and 0.5 mg/kg in a feline endotoxin model

The aim of the trial was to study the antipyretic effect of 3 different doses of Metacam using the established model. Twelve cats were used in the study that was of cross-over design with a wash-out period of 21 days. The general demeanour of each animal was scored every 30 minutes.

All animals showed an increased body temperature following administration of endotoxin, with the highest temperatures occurring after 60-120 min. The meloxicam doses 0.3 and 0.5 mg/kg b.w. showed significant antipyretic effects. The temperatures in these groups were > 1°C lower at 60-120 min. A comparison of the AUCs showed statistically significant differences between the placebo group and the dose groups 0.3 and 0.5 mg/kg b.w. No differences were found between these dose groups.

Changes in general demeanour were not consistent and no differences could be found between the groups. All animals showed the characteristic changes in haematology parameters after endotoxin administration. These changes were not altered by Metacam.

With regard to studies VU-00224 and VU-00219 the marketing authorisation holder argued that it is equally scientifically sound to administer NSAIDs either before or after the pyrogen and that it is not current practice to administer the NSAID after the pyrogen. Reference was also made to five submitted published studies.

Field trials

Metacam 5 mg/ml solution for injection was originally proposed by the marketing authorisation holder for cats as indicated for the reduction of postoperative pain after soft tissue surgery and for the management of febrile conditions. However, based on the studies submitted, the Committee considered that the efficacy of Metacam was provided only for the reduction of post-operative pain after ovariohysterectomy and minor soft tissue surgery.

Perioperative analgesic efficacy of meloxicam compared to carprofen in cats undergoing surgery

The aim of the study was to compare the analgesic effects of meloxicam and carprofen in cats undergoing soft tissue surgery. The reasons for using carprofen as a positive control was that the drug is approved for pain control in some Member states. A total of 80 cats presented for ovariohysterectomy were included in the study. The animals were randomly allocated to two groups and premedicated with acepromazine. The groups were fully comparable concerning age and body weight. Anaesthesia was induced by intravenous injection of thiopentone and maintained by halothane inhalation. Metacam, 0.3 mg/kg b.w. or carprofen, 4 mg/kg b.w., was administered s.c. immediately after induction of anaesthesia. Surgery was performed according to routine procedures. Ampicillin and amoxycillin/clavulanic acid were allowed as antibiotic treatment at the end of surgery.

Rectal temperature, heart and respiratory rate were recorded during and after surgery. Pain and sedation were evaluated using a visual analogue scale (VAS). Blood was collected for analysis of serum cortisol, AST, ALT, creatinine and urea. Seventy-six animals were available for evaluation, 37 in the Metacam group and 39 in the carprofen group. The assessment of pain was considered to be the primary parameter.

Pain and sedation were assessed at extubation and then after 0.5, 1, 2, 4, 6, 8 and 20 hours. The VAS scoring for these parameters did not differ between the groups. The pain score increased after extubation and reached a plateau level after 2 - 4 hours and decreased thereafter. Pain was scored from 0 to 100, where 100 indicates severe pain. The highest pain score in the two groups was 18-19 after extubation, indicating little pain. The VAS scores for sedation decreased constantly after extubation over the whole observation period and reached the pre-surgery level after 20 hours.

Serum cortisol increased by about 50% immediately after surgery in both groups and declined thereafter. There were no significant differences between the groups. Heart rate, respiratory rate and rectal temperature did not differ between the groups during the observation period. No significant differences were found between the groups for the parameters AST, ALT, urea and creatinine. AST was significantly increased from the pre-surgery levels in both groups at 20 h. The increase was more pronounced in the carprofen group.

Metacam 5 mg/ml is approved for reduction of post-surgical pain in dogs, and based on the experience from the dog studies, the marketing authorisation holder chose to use the VAS scoring as the primary parameter in the cat study. The VAS assesses pain according to the evaluator's subjective overall impression. However, the reliability is increased if treatment is blinded as was the case in the present study. Carprofen is approved for pain relief in cats in some Member states and the VAS scores after carprofen and Metacam treatment were found to be equal.

Information was provided (published reports) describing the use of meloxicam in combination with various anaesthetic protocols in dogs. However, whilst there may be no difference between dogs and cats after administration of the proposed doses of meloxicam, safety has only been documented for meloxicam in association with thiopentone/halothane anaesthesia. Given the narrow safety margin of meloxicam in cats and the fact that the clinical experience of NSAIDs in cats is limited, only those treatment protocols for which the safe use has been proven in the target species were deemed to be satisfactory.

Risk-Benefit Assessment and conclusion

The initiation of treatment in the dog can be performed using intravenous, subcutaneous or oral administration at a dose of 0.2 mg/kg body weight. Thereafter, the maintenance dose is 0.1 mg/kg body weight restricted to oral administration.

The bioavailability after both oral and subcutaneous administration is 100%. No significant accumulation of meloxicam occurred after repeated treatment with the recommended posology. The local tolerance after parenteral administration was studied in laboratory animals and in the target species. Subcutaneous injection of Metacam solution for injection to rabbits resulted in minor macroscopic and microscopic changes. Reddening of the musculature, small focal haemorrhages in subcutis and necrosis of single myofibres were the most prominent findings. Similar changes were found in the control group injected with physiological saline. Similar findings were obtained also after i.m. injection of Metacam. Slight focal skin epithelial necrosis and focal necrosis of muscle fibres were found. Metacam solution for injection was well tolerated in dogs except for slight pain reactions in single individuals. No inflammatory reactions were noted.

Metacam solution for injection is indicated for use in individual companion animals. No further data were considered necessary and the environmental risk assessment was concluded in Phase I.

The use of Metacam 5 mg/ml solution for injection in a single dose of 0.2 mg/kg followed by Metacam 1.5 mg/ml oral suspension in the dose 0.1 mg/kg daily is well documented in a number of studies of sufficient size for treatment of acute and chronic inflammatory and painful processes in muscles and skeleton in the dog.

Metacam 5 mg/ml is indicated in dogs for alleviation of pain in both acute and chronic musculo-skeletal disorders and for reduction of post-operative pain and inflammation following orthopaedic and soft tissue surgery. The proposed dose in cats is 0.3 mg/kg b.w. given subcutaneously as a single treatment. Oral follow up therapy with meloxicam or other NSAIDS cannot be recommended in cats, as no safe dosage for repeated oral administration has been established.

Pharmacokinetics of meloxicam was studied in cats after intravenous, subcutaneous and oral administration of the proposed dose. Bioavailability after subcutaneous administration was 100%. Major pharmacokinetic parameters were similar after all routes of administration. The elimination

half-life, 14-16 hours, was shorter than in dogs. The binding to plasma proteins was high. Pharmacokinetics were studied only after single dose administration, but this was regarded as sufficient as a claim is made for single treatment only.

The local tolerance of Metacam 5 mg/ml was extensively studied in laboratory animals and in dogs, in the studies included in the original application. Subcutaneous injection to rabbits resulted in minor macroscopic and microscopic changes. Reddening of the musculature, small focal haemorrhages in subcutis and necrosis of single myofibres were the most prominent findings. Similar changes were found in the control group injected with physiological saline. Metacam 5 mg/ml solution for injection was well tolerated in cats and dogs except for slight pain reactions in individual dogs. Local tolerance was also investigated during the study on target animal safety.

As is the case with other NSAIDs, the results of the submitted tolerance studies show that cats are very sensitive to the gastro-intestinal and renal effects of meloxicam. However, no clinical or histopathological adverse reactions occurred after subcutaneous treatment with the proposed dose (0.3 mg/kg b.w.) for three days. The proposed single treatment with 0.3 mg/kg b.w. was therefore considered as safe.

Safety was not documented in pregnant and lactating animals and therefore an appropriate contra-indication has been included in the SPC in addition to the contraindication for use in animals of less than 2 kg or of less than 6 weeks of age.

Pain relief was studied in the post-surgical period after ovariohysterectomy. The CVMP decided, on the basis of the data submitted that the indication for the product in cats should be the reduction of post-operative pain after ovariohysterectomy and minor soft tissue surgery.

V METACAM 1.5 MG/ML ORAL SUSPENSION FOR DOGS, METACAM 0.5 MG/ML ORAL SUSPENSION FOR DOGS AND METACAM 0.5 MG/ML ORAL SUSPENSION FOR CATS

Metacam 1.5 mg/ml oral suspension for dogs is presented in polyethylene bottles containing 10, 32, 100 or 180 ml with sodium benzoate as preservative. Initial treatment is a single dose of 0.2 mg meloxicam/kg body weight on the first day. Treatment is to be continued once daily by oral administration (at 24-hour intervals) at a maintenance dose of 0.1 mg meloxicam/kg body weight.
For longer treatment, once clinical response has been observed (after ≥ 4 days), the dose of Metacam can be adjusted to the lowest effective individual dose reflecting that the degree of pain and inflammation associated with chronic musculo-skeletal disorders may vary over time. To be administered orally either mixed with food or directly into the mouth. Alternatively therapy may be initiated with Metacam 5 mg/ml solution for injection.

Metacam 0.5 mg/ml oral suspension for dogs is presented in polyethylene bottles containing 15 or 30 ml with sodium benzoate as preservative. Initial treatment is a single oral dose of 0.2 mg meloxicam/kg body weight on the first day. Treatment is to be continued once daily by oral administration (at 24-hour intervals) at a maintenance dose of 0.1 mg meloxicam/kg body weight. For longer treatment, once clinical response has been observed (after ≥ 4 days), the dose of Metacam can be adjusted to the lowest effective individual dose reflecting that the degree of pain and inflammation associated with chronic musculo-skeletal disorders may vary over time. To be administered orally either mixed with food or directly into the mouth. Alternatively therapy may be initiated with Metacam 5 mg/ml solution for injection.

Metacam 0.5 mg/ml oral suspension for cats is presented in polyethylene bottles containing 15 ml with sodium benzoate as preservative. Initial treatment is a single oral dose of 0.1 mg meloxicam/kg body weight on the first day. Treatment is to be continued once daily by oral administration (at 24-hour intervals) at a maintenance dose of 0.05 mg meloxicam/kg body weight. The maintenance dose of 0.05 mg meloxicam/kg body weight can also be used for follow-up treatment after initial treatment with Metacam 2 mg/ml solution for injection. To be administered orally either mixed with food or directly into the mouth.

QUALITY ASSESSMENT

Composition

Metacam 1.5 mg/ml oral suspension for dogs

Meloxicam	1.5 mg/ml	B.P.
Sodium benzoate	1.5 mg/ml	Ph. Eur.

Metacam 0.5 mg/ml oral suspension for dogs

Meloxicam	0.5 mg/ml	B.P.
Sodium benzoate	1.5 mg/ml	Ph. Eur.

Metacam 0.5 mg/ml oral suspension for cats

Meloxicam	0.5 mg/ml	B.P.
Sodium benzoate	1.5 mg/ml	Ph. Eur.

Container

Metacam 1.5 mg/ml oral suspension for dogs is packed in a plastic screw necked bottle with dropper and screw closure having an original tamper- proof child resistant closure and a 5 ml oral syringe with

an integrated adapter and with a “kg/body weight” graduation. Pack sizes: 10 ml (in a 25 ml bottle), 32 ml (in a 39 ml bottle), 100 ml (in a 115 ml bottle) and 180 ml (in a 315 ml bottle).

Metacam 0.5 mg/ml oral suspension for dogs is packed in a plastic screw necked bottle with dropper and screw closure having an original tamper- proof child resistant closure and a 3 ml oral syringe with an integrated adapter and with a “kg/body weight“ graduation. Pack size: 15 ml (in a 25 ml bottle) and 30 ml (in a 39 ml bottle)

Metacam 0.5 mg/ml oral suspension for cats is packed in a plastic screw necked bottle with dropper and screw closure having an original tamper- proof child resistant closure and a 1 ml oral syringe with an integrated adapter and with a “kg/body weight“ graduation. Pack size: 15 ml (in a 25 ml bottle).

Clinical trial formulations

For Metacam 1.5 mg/ml oral suspension for dogs, the clinical trial formula is the formula that since earlier has been introduced on the market, under the trade name Metacam, in most of the European countries.

The equivalence between the clinical trial formula for dogs and the formula intended for marketing has been demonstrated in-vitro. The absolute bioavailability in vivo (6 beagle dogs) of the clinical trial was shown to be 100% compared to i.v. administration. Both formulations show the same in vitro dissolution profile.

For Metacam 0.5 mg/ml oral suspension for dogs, the equivalence between the clinical trial formula and the formula intended for marketing has also been demonstrated.

For Metacam 0.5 mg/ml oral suspension for cats, the clinical trial formula is identical to the formula intended for marketing.

Product Development Studies

Meloxicam is sufficiently soluble in alkaline medium to form a solution. A solution is unstable and has a very bitter taste and therefore an aqueous suspension of meloxicam, intended to replace the currently marketed suspension, was developed. The formulation currently marketed is the formulation used in the clinical trial.
Sodium benzoate is used as preservative. The chosen concentration preserves the suspension in accordance with the requirements of Ph. Eur.

The development studies including the changes from the currently marketed formulation to obtain the proposed formulation are well described and sufficiently motivated. Meloxicam is subjected to a full analysis according to the specification. In-vitro dissolution studies have demonstrated that both formulations show the same in vitro dissolution profile. Thus, sufficient evidence for expected bio-equivalence between the formulations has been presented.

The recent manufacturing process is a standard procedure using conventional techniques. The critical process parameters have been identified and limits have been set. The release specifications for finished product are considered acceptable and the batch analysis results confirm that the product has an acceptable quality. The number of bottles checked for the filling volume by each batch in the in-process control is acceptable and validation data of the manufacturing process has been provided.
The process development for Metacam 0.5 mg/ml was also described in detail. In vitro comparison of the two strengths was described in detail and found to be satisfactory.

For Metacam 1.5 mg/ml oral suspension the dropper providing 0.05 mg of meloxicam per drop, i.e. 2 drops per kg body weight of the maintenance dose and a child resistant bottle closure have been introduced. The new dropper shows accuracy according Ph. Eur. The packaging material is unchanged.

In the case of Metacam 0.5 mg/ml oral suspension for dogs the dropper provides 0.02 mg meloxicam per drop, i.e. 5 drops per kg body weight of the maintenance dose.

In the case of Metacam 0.5 mg/ml oral suspension for cats the dropper provides 0.017 mg meloxicam per drop, i.e. 3 drops per kg/body weight of the maintenance dose.

DESCRIPTION OF METHOD OF PREPARATION
Manufacturing chain

Boehringer Ingelheim Pharma GmbH & Co. KG, 55216 Ingelheim, Germany, Biberach an der Riβ site, was the manufacturer of the finished veterinary product and was also in charge of batch release in the EEA. In a subsequent variation, the site of finished product manufacture was transferred to Boehringer Ingelheim Vetmedica Inc., 15 & Oak, Elwood, Kansas, USA. The site for batch release was transferred to Boehringer Ingelheim Vetmedica GmbH, Binger Straβe 173, 55216 Ingelheim, Germany.
Manufacturing process

Metacam 1.5 mg/ml oral suspension
The manufacturing formula was presented. The typical batch-size is 1000 kg. The manufacturing process was presented in a flow diagram. The process is a standard process using conventional techniques. In- process controls are performed and the in-process specifications are presented.
The manufacturing process including the in-process controls is considered acceptably well described.

Metacam 0.5 mg/ml oral suspension
The intended batch size is 500 kg or 1000 kg. The processes were appropriately presented and found to be acceptable.

Validation of the process

The validation of the process was presented. The manufacturing process is a standard procedure using conventional techniques. The critical process parameters have been identified and limits set. Batch results have been presented and the results confirm that the process would lead to a product meeting the stated requirements. This is also applicable to Metacam 0.5 mg/ml oral suspension.

Packaging material

The packaging materials have been described. Plastic screw-necked bottles with dropper and screw closure having an original tamper proof seal. An oral syringe with an integrated adapter and with a "kg/body weight" graduation is also provided. The types of material used for the different parts of the primary packing are specified. The compositions of the used starting materials comply with recommendations of the Federal Health Authorities of the Federal Republic of Germany, the Code of Federal Regulations and the Ph. Eur. Analytical and chemical testing specifications are given.

The measuring syringe and the dropper have been tested with respect to dosing accuracy according to the requirements of Ph. Eur. The studies were performed with the formulation used in the clinical studies. The results show that the requirements of Ph. Eur. were fulfilled. As the compositions of the formula used in the clinical studies and the formula proposed for marketing are quite similar the results from the report are considered acceptable.

The products Metacam 0.5 mg/ml oral suspension for dogs and Metacam 0.5 mg/ml oral suspension for cats are identical with respect to the formula of the suspension as well as the immediate packaging material. Acceptable specifications for the used materials have been provided.

A report on the dosing accuracy of the measuring syringe and of the dropper was provided. The test is performed in accordance with the requirements stated in the Ph. Eur.

Due to the fact that domestic cats usually have smaller body weights than dogs, the size of the added dropper and of the measuring syringe have been adjusted. The product for dogs contains a 3 ml measuring syringe and the product for cats is supplied with a 1 ml measuring syringe.

A mix-up of the two different products is prevented as the products are labelled specifying the target species; the size of the measuring syringe (1 ml versus 3 ml) differs so that the two products are very clearly differentiated and the syringes are marked with a pictogram (dog or cat).

With regard to the possibility of a mix-up of droppers at the manufacturing site, this can be excluded as the production of this product takes place under controlled GMP conditions.

CONTROL TESTS OF THE ACTIVE SUBSTANCE

Meloxicam is tested according to the British Pharmacopoeia with additional in house tests.

CONTROL TESTS OF THE FINISHED PRODUCT

Specification and routine testing

The quality of both Metacam 0.5 mg/ml oral suspension and Metacam 1.5 mg/ml oral suspension at release and throughout their respective shelf-lives was assured by the proposed analytical methods.

Validation

The validation of the analytical methods was presented. The UV-VIS identification test mentioned is the TLC method as described. The HPLC method used for identification, assay of sodium benzoate, meloxicam and for the determination of the decomposition of active ingredient has been validated. The assay methods have been validated in respect to specificity, linearity, accuracy, ranges of parameters for linearity, accuracy, repeatability, intermediate precision and robustness. The validation parameter for identity is specificity. Validation parameters performed for the degradation determination method are specificity, quantification limit, linearity, accuracy, repeatability (ranges of parameters for linearity, accuracy, repeatability) and robustness. The validation was considered acceptable.

Batch analysis

Results of batch analysis were presented. Since these batches were tested, the test for extractable volume has been exchanged to be performed by weight, a second identification test for meloxicam and a test for homogeneity during filling have been included. All results presented are within the stated specifications.

STABILITY

Stability studies on active substance

Data have been provided to allow a re-test period of 5 years for the active ingredient.

Stability tests on the finished product

Metacam 1.5 mg/ml oral suspension

Stability tests on the finished product were presented. Parameters studied are appearance, odour, pH, redispersibility, particle size, viscosity, microbiological characteristics, assay and degradation of meloxicam, assay of sodium benzoate and packaging characteristics (appearance and function). The methods used are in accordance with the testing specification for the finished product. The sodium benzoate content decreased depending on storage time, temperature and container size. The results were within the shelf-life limits. No other relevant changes were observed.

The presented stability test results for the finished product demonstrate acceptable stability for up to 19 months at 25°C/60 %RH and 30°C/70%RH. In addition, results form storage at 6 months at 4°C and 40°C/75 %RH have been supplied. The proposed shelf-life limit for the finished product content

of meloxicam is 95-105% and has been accepted by the marketing authorisation holder for both release and shelf-life specification. All results are within the specification limits. The proposed shelf-life of 2 years is therefore acceptable with no special precautions for storage. Subsequently, the shelf life has been extended to 3 years.

Metacam 0.5 mg/ml oral suspension

The proposed shelf-life of 5 years was accepted.

In-use stability

The presented in-use stability test has shown that a shelf- life of 6 months after first opening can be accepted. A preservative efficacy test has been performed and acceptably demonstrated that preservation is assured at least down to 75% sodium benzoate. Results from a light exposure test have been submitted. In conclusion the proposed "no special precautions for storage" is considered acceptable.

Preservative efficacy test

This test was performed with the samples from the in-use stability test after dispensing and after storage at 6 months at 25°C, 60 RH %. The results comply with the United States Pharmacopoeia (USP) and the European Pharmacopoeia (Ph. Eur.).

Photo-stability

A light exposure test was performed on the pack-size 10 ml in the polyethylene bottles intended for marketing and for comparison in colourless glass flasks (not intended for marketing). Light exposure was 22 hours of Xenon light. In addition the containers were wrapped in aluminium foil. Parameters tested were: appearance, odour, pH, redispersibility, particle size, viscosity, degradation, assay of meloxicam and of sodium benzoate. Degradation was only observed in the un-wrapped glass flasks. No other relevant changes were observed. The proposed "no special precautions for storage" is considered acceptable.

SAFETY ASSESSMENT
Pharmacokinetics

A pilot study was performed in one male and one female mini-pig. Both animals were given 3.5 mg/kg of ^{14}C-labelled meloxicam orally. The distribution of total radioactivity was studied after 4 hours. High radioactivity was found in kidney and liver. Low activity occurred in the brain, indicating the existence of a blood/brain barrier for meloxicam. The plasma/tissue ratios were high, indicating a low volume of distribution of the drug or its metabolites.

The parent compound dominated in plasma. The reverse situation occurred in urine and bile, where the contribution to the total radioactivity by the parent compound was less than 3%. The major metabolites, an acid and an alcohol were identified in earlier studies. The in vivo protein binding was about 96%.

The total recovery of radioactivity after analysis of tissues and excreta was 82% in the male and 71% in the female. Considerable radioactivity was found in urine (17-31%) and in faeces (2-9%).

Biliary elimination proceeded in a continuous manner. About 60% of the dose was eliminated in faeces during 96 hours after treatment. Faecal excretion was not completed by this point, and was calculated to proceed for a further 2 days. Renal elimination accounted for about 25% of the administered dose and was largely completed after 96 hours. The mean elimination half-life was similar after all routes of administration, about 24 h with a range from 17 to 36 h. No major differences were observed for the other parameters, except for C_{max} and T_{max} after oral and s.c.

administration. C_{max} was 0.464 ± 0.059 µg/ml after oral administration and 0.734 ± 0.117 µg/ml after s.c. injection. The corresponding figures for T_{max} were 7.5 h and 2.5 h.

The bioavailability of meloxicam in dogs after both oral and s.c. administration is 100%. The metabolite profiles in bile and urine are in line with earlier results obtained in other species and the elimination takes place largely via the bile. Plasma protein binding was high which should be borne in mind as regards possible interactions. This item is adequately covered in the SPC.

Determination of meloxicam in cat plasma

The validated analytical method was presented and consisted of liquid/liquid extraction analysed by reverse-phase HPLC with UV detection. The method was found to perform satisfactorily. This method is principally the same as the one used previously for cat plasma, however it was validated at lower concentrations. Long term stability was not investigated here but was demonstrated previously.

Pharmacokinetics of Metacam oral suspension 0.5 mg/ml after oral administration to cats

A GLP-compliant study was carried out and a dose-related linear exposure noted. The pharmacokinetic parameters were presented and no adverse reactions were recorded during the study period. It was concluded that the pharmacokinetic profile of meloxicam in cats after repeated oral administration is as expected based on previous available data in cats. Furthermore, no major differences between cats and dogs were noted.

Pharmacokinetics of Metacam 0.5 mg/ml oral suspension after oral administration to fed and fasted cats.

This was a single dose, two period cross-over study. Pharmacokinetic parameters were calculated using non-compartment analysis. No clinically relevant differences in pharmacokinetic parameters including bioavailability were recorded and no adverse reactions were recorded during the study period. Metacam can be administered either mixed with food or directly into the mouth. This is found acceptable based on the data provided.

User safety

In a Magnus and Kligman test with a gel formulation there was no evidence of a sensitisation reaction. Similarly, no sensitisation reaction was reported with placebo gel, but a positive reaction was found with a 0.3% DNCB formulation. In an ocular irritation test no potential for ocular irritation was noted with a formulation including meloxicam at a concentration of 0.5%. The formulation tested differed however in the content of excipients from the applied formulations and some of the excipients were not included.

There were no remarkable findings regarding clinical signs, changes in body weight, haematology, clinical chemistry, and urinalysis when applied topically to rabbits. There were also no reported adverse effects revealed at (thorough) autopsy, including a lack of findings at the site of application. Thus, it appears that meloxicam in topical solution was without local as well as systemic effects in this study. The dermal absorption of meloxicam was 5-30% of that absorbed orally.

Whilst the composition of the formulation tested for dermal irritation was not identical to the applied oral formulation. It is, however, considered unlikely that the other excipients contained in Metacam oral suspension should cause dermal irritation in the volumes used in clinical practice.

Conclusion on user safety

In rabbits, meloxicam showed no potential for causing dermal irritation after topical administration in a gel formulation for 28 days in a dose of 5 mg/rabbit, with a maximum estimated absorption of 30%. There was no evidence of a sensitisation reaction in guinea pigs of a gel formulation containing 1% meloxicam. There was no potential for ocular irritation of meloxicam administered as an eye drop

formulation, not identical to the applied formulations, in doses up to 0.5%. A warning concerning individuals sensitive to NSAIDS has been included in the SPC.

Environmental risk assessment

The criteria laid down in the Phase I decision tree in the CVMP Note for Guidance EMEA/CVMP/055/96-FINAL on environmental risk assessment implicates that veterinary medicinal products indicated for use in companion animals are to be exempted from a Phase II assessment. Furthermore, Metacam 1.5 mg/ml oral suspension and Metacam 0.5 mg/ml oral suspension are indicated for use in individual animals. No further data are considered necessary and the environmental risk assessment is concluded at Phase I.

CLINICAL ASSESSMENT
Tolerance in the target species (dogs)

The tolerance of 0.2 mg/kg b.w. of meloxicam given as a daily oral dose for 4 weeks was studied in healthy Beagles. The age of the dogs used in the study varied from 1.5 to 13 years. Slight fluctuations in appetite and changes in faecal consistency were observed in some dogs after the dose 0.2 mg/kg/day. Occult blood was detected in faeces and persisted for 1-3 days in all dogs except two. The higher dose, 0.3 mg/kg/day appeared to cause more severe gastro-intestinal symptoms. The appearance of occult blood in faeces persisted longer than after the lower dose. Several dogs of group B showed haemorrhagic gastro-enteritis at the end of the study. The test for parvovirus was positive which made the interpretation of the results more difficult.

Whilst no certain conclusion can be drawn, the results indicate that meloxicam may induce symptoms from the gastro-intestinal tract.

No clinical signs occurred during the treatment period. Both test kits for blood in faeces showed positive results for individual animals from week 2 until sacrifice, but no relevant differences between the control group and the treated groups occurred. The authors concluded that the value of the test could be questioned, as there were no signs of gastrointestinal lesions at autopsy. No macroscopical or microscopical lesions were found in the kidneys or in other organs. No treatment related changes were found in any of the studied clinical chemistry parameters.

Beagles, aged 6-8 months, were included in a target animal tolerance study. The body weights varied from 6.95 kg to 9.85 kg. The dogs were allocated to 4 groups. The dogs were given a single subcutaneous injection of Metacam and were thereafter treated orally with the Metacam oral suspension for the following 6 days. The subcutaneous doses were 0, 0.2 mg/kg, 0.4 mg/kg, and 0.6 mg/kg. The oral dose was 0.1 mg/kg. The animals were treated about 30 min. after the morning feeding. Clinical signs, body weights, food and water consumption were recorded. All dogs were autopsied after a recovery period of 7 days. No clinical signs occurred and body weights, food and water consumption remained unaffected. Faeces were tested for the presence of occult blood. A positive result was seen in one female of the control group on day 4, and in one male of the intermediate dose group on day 5. All other samples were negative.

All changes were considered to be consistent with the expected background pattern of observations in dogs of this breed and age. No consistent changes that could be related to treatment occurred in the studied haematological and clinical chemistry parameters.

Dogs are known to be very sensitive to the ulcerogenic effect of NSAIDs. The presence of blood in faeces was carefully tested and only two positive samples were found, one of the samples was found in the placebo group. No signs of ulceration or haemorrhages in the gastro-intestinal tract were found at necropsy. Thus, the treatment appeared to be well tolerated.

Transient gastro-intestinal symptoms, e.g. vomiting, soft stool and diarrhoea occurred in the dogs during the acclimation period before treatment as well as after treatment However, the authors found it

difficult to relate the symptoms to treatment, since transient symptoms occurred also during the wash-out periods. The general impression was that meloxicam was well tolerated.

Tolerance in the target species (cats)

Two GLP studies were presented.

In the first, cats meeting the selection criteria were assigned to four study groups. Veterinary and general examinations were performed and haematological/clinical chemical analyses and necropsy were carried out. It was concluded that meloxicam (Metacam 0.5 mg/ml oral suspension) was well tolerated in adult cats following repeat dosing for 90 days at the normal recommended dose, three times the normal recommended dose and five times the normal recommended dose.

Effects were mainly related to the gastrointestinal system. Pathology revealed effects mainly in the gastrointestinal system with gastric and duodenal ulcer in the 3x (0.3 + 0.15 mg/kg) and 5x (0.5 + 0.25 mg/kg) group. Pale mucous membranes, melaena, black/dark faeces and low haemoglobin, haematocrit and APTT, suggest that bleeding occurred. These effects could be expected, since they are typical of an NSAID. Notably, there were no NSAID-related effects on kidneys recorded in this study. The mean increase in weight in all the groups is assumed to be due to the low age of the animals.

In a second study, to obtain information on the tolerance of meloxicam (Metacam 1.5 mg/ml oral suspension) when given by oral administration (gavage) to cats for 14 consecutive test days, animals were placed in one of four groups (1 placebo group and 3 treatment groups [0.025, 0.05 and 0.1 mg/kg meloxicam respectively]) . Haematological and biochemical parameters were assessed prior to the onset of the study.

There were broad intra-individual and inter-individual variations for the results obtained in all groups, but values were within the accepted normal ranges (when available). There were no significant differences between groups for clinical signs and physical examination, body temperature, bodyweight, diet consumption, faecal occult blood, haematology, clinical chemistry or macroscopic and microscopic pathological findings that were treatment dependant and of importance to the aims of the study.

Under the conditions of this study, the daily oral administration of meloxicam at dose levels of 0.025, 0.05 and 0.1 mg/kg body weight for a treatment period of 14 days did not produce any histopathological evidence of a toxic effect of the test substance, in either sex. There were no significant test substance related side effects observed in the present study using meloxicam (Metacam 1.5 mg/ml oral suspension) at doses up to and including 0.1 mg/kg bodyweight orally once daily on an empty stomach in cats for 14 consecutive days. The no adverse effect level in this study was 0.1 mg/kg bodyweight meloxicam.

Clinical Studies (dogs)

Ten studies were conducted to support the claim of “alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders. Some trials were exploratory in nature and therefore could only be considered as supportive.

Metacam 1.5 mg/ml oral suspension

Clinical efficacy and tolerance of Metacam for long-term treatment of chronic canine locomotor disorders

Sixty-two dogs with chronic locomotor disorders were randomly allocated to two treatment groups. Group A was given an oral meloxicam dose of 0.2 mg/kg b.w. for a period of 21 days, thereafter the dose was reduced by 50%. Group B was given 0.2 mg/kg for 7 days followed by a 50% dose reduction. The treatment period was 3 months in both groups.

Clinical examination was performed on day 1, day 7, day 21 and after 3 months. A general and a more specific locomotor examination was performed at each occasion.

Blood samples for routine haematological and clinical chemistry investigation were collected before treatment, after 3 weeks and after 3 months.

The mean scores for the specific locomotor parameters improved in a similar way in the two groups from the first to the last clinical examination. No differences between the groups could be seen. The mean mobility score representing the sum of the locomotor parameters was calculated for each group. Both groups improved significantly, but no differences between the groups occurred. Eleven cases of adverse reactions were observed, 6 in group A and 5 in group B. Most cases occurred during the first 8 days of treatment. Vomiting was the dominating symptom (5 cases). Other symptoms were diarrhoea, polydipsia, ataxia and dermatitis. All cases were rather mild and specific treatment was not required. The symptoms disappeared during the course of treatment.

The conclusion of the study was that the used doses of meloxicam was safe and effective for the long-term treatment of locomotor disorders in dogs, and further that the initial dose of 0.2 mg/kg b.w. may be reduced by 50% after 7 days.

Clinical efficacy and tolerance of two parenteral meloxicam (Metacam) formulations given as single s.c. injections followed by subsequent oral treatment with meloxicam (Metacam) in dogs with acute locomotor disorders.

The aim of this trial was to study safety and efficacy in dogs with acute locomotor disorders. Only dogs that had shown symptoms for less than 14 days were included. Dogs that had been treated with steroids or NSAIDs within a period of 2 weeks prior to the trial were excluded, as were pregnant females and females in heat. A total of 65 dogs were recruited to the study. Several breeds and cross-breeds were included and the age of the dogs varied from 5 months to 15 years.

The study was performed at 3 different centres. The dogs were randomly allocated to two treatment groups. After a thorough clinical examination, all dogs were given a subcutaneous injection of meloxicam at the dose 0.2 mg/kg followed by oral treatment with the same dose for up to one week. The only difference between the groups was that a multi-dose vial of the injection formulation was used in group A, while 1 ml ampoules were used in group B. Body weight, rectal temperature and general demeanour were recorded during the study. Some special parameters for defining the locomotor disorder were scored. After the clinical examination at recruitment, the investigator defined the affected body area. If considered necessary, X-ray examination was performed.

Thirty-one dogs in each group were evaluated. The mean age in the two treatment groups was 5.9±4.26 years and 6.2±4.12 years. The mean body weights were 22.9±13.4 kg and 27.7±15.0 kg. The sex ratio was similar in both groups. Very few young dogs were included, only 4 dogs were less than one year old in group A, and 2 in group B. The most common diagnoses were contusions/sprain caused by trauma and acute arthrosis or arthritis.

The mean scores for the specific locomotor parameters under the course of therapy were provided. The score mean for all parameters were significantly lower on day 6 than on day 1. The overall clinical response was judged as Excellent/Good in 96% of the dogs in group A and in 90.8% in group B on day 6.

The adverse reactions were few, a single case of vomiting and one case of diarrhoea were observed in group B. One dog in group A showed transient vomiting and diarrhoea. Additional therapy was not considered necessary and the medication with Meloxicam was not discontinued.

The suggested dosage was not used in this uncontrolled study. Both groups were treated in the same way, and as expected both groups responded similarly. However, the results are adequately described and discussed. Very few young dogs were included.

Placebo-controlled study on clinical efficacy and tolerance of a single subcutaneous injection of meloxicam (Metacam) followed by oral treatment over 6 consecutive days in acute canine locomotor disorders.

A blinded and placebo-controlled study was performed at four different centres in Germany. The inclusion and exclusion criteria were identical with those in the preceding study. A total of 89 dogs were recruited to the study. The dogs were randomly allocated to two treatment groups. One group was given a subcutaneous injection of 0.2 mg/kg on the first day of treatment, the other group was given placebo. Thereafter, all dogs in both groups were treated orally with 0.2 mg/kg for the following 6 consecutive days. According to the protocol, the dog owners were instructed to administer the oral suspension in the mornings in a small amount of the dogs favourite food.

Forty-six dogs in the full treatment group and 41 in the placebo/meloxicam group were available for evaluation. One dog in each group was lost.

The included dogs were of different breeds. The mean body weight was 27.3±15.9 in the full treatment group and 28.8±14.8 in the control group. The mean age was 6.3±6.55 kg and 7.0±4.42. A total of 8 dogs less than one year old were included. The dominating diagnosis was arthropathies.

The special locomotor parameters were scored. Clinical examination was performed before inclusion and then on days 1, 2 and 8. The scores for the studied parameters on the selected time points were provided. Improvement was achieved of all the studied parameters within both groups. A statistical comparison was made between the groups, a small but significant difference ($p < 0.05$) occurred between the scores for motionless weight-bearing, locomotion and local inflammation on day 8. An evaluation of the overall clinical response in both groups was also presented.

The differences between the groups were not statistically significant, but were seen as a confirmation of the results obtained for the special locomotor parameters.

Eleven cases of adverse reactions were observed. Gastro-intestinal signs, vomiting and diarrhoea, occurred in 4 dogs. The signs were considered as mild and transient. Other observed signs were polydipsia and polyphagia. Special treatments of the adverse reactions were not considered necessary.

Additional therapy was given to 7 dogs by one investigator. However, the additional treatment was given for skin disorders, hormonal deficiencies and cardiovascular diseases and were not considered to be relevant for the clinical evaluation.

The difference in clinical response in the two groups was small, but statistically significant for some locomotor parameters. The difference was most evident after 8 days. It was considered rather unlikely that one additional treatment compared with the control group was the only explanation. Very early treatment under the supervision of a veterinarian was considered to be the most probable explanation of the difference in response between the groups.

Clinical efficacy and tolerance of a reduced dose level for meloxicam (single dose of 0.2 mg/kg followed by 0.1 mg/kg once daily) versus the established once-daily dose of 0.2 mg/kg for 7 days of treatment in dogs with acute locomotor disorders.

The aim of the study was to compare the clinical efficacy and tolerance of 3 different meloxicam treatment schedules in dogs suffering from acute locomotor disorders in order to investigate the therapeutic implications of an early dose reduction from 0.2 mg/kg to 0.1 mg/kg from the second day of treatment. Clinical cases of acute locomotor disorders were recruited to the study. Dogs showing symptoms for more than 14 days were not included. Females in heat and pregnant bitches were excluded as were also cases of diabetes mellitus, osteoporosis, febrile reactions and fractures. The dogs were randomly allocated to 3 different treatment groups:

Group A Once daily oral administration of 0.2 mg meloxicam/kg b.w. for 7 days

Group B A single oral administration of 0.2 mg meloxicam/kg b.w. on day 1 followed by 6 daily oral doses of 0.1 mg/kg).

Group C A single subcutaneous injection of 0.2 mg meloxicam/kg b.w. on day 1 followed by 6 daily oral doses of 0.1 mg/kg.

The mean scores for mobility, local inflammation and palpatory pain were comparable in each group on day 1 and were reduced at each clinical examination. The lowest scores were obtained on day 8. No differences could be found between the groups. The number of dogs with disturbed general demeanour decreased during the observation period, and more than 90% of the dogs in each group showed undisturbed demeanour on day 8. Evaluation of the overall clinical efficacy showed that treatment groups A, B and C produced excellent/good scores of 88.4%, 87.9% and 95.3% respectively.

No adverse reactions could be observed after subcutaneous injection in group C. Four cases of vomiting and diarrhoea occurred in group A, the symptoms were not severe and were characterised as single events. One case occurred in group B. The dose was reduced in order to reduce the risk of adverse reactions. The number of treated dogs is sufficient for valid conclusions. The results showed that the dose could be reduced without loss of therapeutic activity. However, the last clinical examination was performed on day 8, e.g. one day after completed treatment and the study gave no indications on the risk for relapses.

Clinical efficacy and tolerance of Metacam (meloxicam) during a 28-day oral treatment period in dogs suffering from chronic locomotor disorders.

Fifty-seven dogs suffering from chronic locomotor disorders were originally recruited to the study and 50 were available for the final evaluation. A chronic locomotor disorder was defined as a change in the gait, painful or not, which had persisted for at least 3 weeks. The exclusion criteria were identical to those in the previous efficacy studies. The trial was conducted as a randomised placebo controlled multi-centre study. The dogs were allocated to two treatment groups: Metacam (group A) and placebo (group B).

A clinical assessment was made for each dog on days 1, 7, 28 and 42. The following parameters were scored at each clinical examination: general demeanour, feed intake, lameness, palpatory pain, stiffness, painful rise and general mobility. The overall effect of treatment was scored. Metacam or placebo product was administered by the dog owners for a period of 28 days. The dose was 0.2 mg/kg orally on day 1, followed by 0.1 mg/kg orally on the subsequent 27 days. Blood was collected on days 1 and 28 and urea and creatinine were analysed for evaluation of the renal function.

The mean age of the dogs in group A was 11.2 years and in group B 10.5 years. The mean body weights were 29 kg and 29.5 kg, respectively, indicating that most of the dogs were of larger breeds. The dogs in group A had shown symptoms for 22.2 months and the dogs in group B for 19.5 months. The most frequent diagnoses were arthrosis and arthrosis+dysplasia. The treatment groups were compared using one-sided Fischer's exact tests. The numbers of animals showing improvement in the components of the global score on days 7, 28 and 42 in comparison with the pre-treatment value were presented. In order to investigate the extent of relapses between days 28 and 42, the global scores for these time points were compared. The global score is the sum of the scores for lameness, palpatory pain, stiffness and painful rise.

Treatment group	**Day 28**	**Day 42**	**Difference**
Metacam	7.29	8.09	$p<0.05$
Placebo	8.25	8.89	$p<0.05$

As shown in the table, relapses occurred and the global scores were significantly higher in both groups on day 42. The change of the individual components of the global score was statistically significant only with respect to the assessment for lameness. The change in lameness score was significant in both groups. Adverse reactions were reported in both groups. Seven cases of vomiting and diarrhoea occurred in the Metacam group and 8 in the placebo group. Constipation occurred in one dog in the Metacam group and in 3 dogs in the placebo group. Other reported signs were reduced appetite, dysuria, respiratory signs and changed behaviour. Adverse events were reported in 31% of the dogs in the Metacam group and in 44% in the placebo group.

Treatment did not change the blood concentrations of urea and creatinine, indicating that renal function was not impaired. The values for these parameters were at the upper physiological limit at initiation of treatment, which can be considered as normal for older dogs. The dogs recruited to the study were old and of larger breeds, and suffering from locomotor diseases typical for that category of animals. The study was well conducted and reported.

Treatment appeared to be well tolerated and no serious adverse reactions were observed. The number of reported adverse reactions was high in both groups. However, most of the non-gastrointestinal signs were obviously not treatment related. The study was blinded and the assessment of clinical efficacy was based on subjective opinions. The placebo effect was unexpectedly high, 40%. There was a significant difference in global score between the groups, but not in the individual components of the global score, e.g. lameness and stiffness, due to a wide individual variation. The difference between the Metacam and the placebo group was not large, but the results are acceptable when taking into consideration that the dogs had shown symptoms for more than a year.

Clinical evaluation of Metacam suspension; determination of clinical efficacy and tolerance in dogs suffering from chronic locomotor disorders

Thirty-eight dogs with diagnosed chronic locomotor disorders were randomly allocated to two equal treatment groups. During the first phase of the study, dogs in one group were treated with 0.2 mg/kg of meloxicam on the first day and thereafter with 0.1 mg/kg daily for the following 6 days. The other group was treated with placebo. On day 8, the dogs in the placebo group were given 0.2 mg/kg of meloxicam and thereafter 0.1 mg/kg/day, the medication with 0.1 mg/kg/day continued in the first group. The study was terminated after 28 days. Metacam oral suspension was given in a small amount of the morning feed.

Body weight, rectal temperature, feed intake, and general demeanour were monitored on days 1, 7, and 28. The special parameters for locomotion: lameness, stiffness, painful rise, exercise intolerance and quality of life were scored independently by the investigating veterinarian and the dog owners on the same days. Body weight, temperature and feed intake remained unchanged during the observation period. The veterinarians and the dog owners came to similar conclusions regarding the scores for the locomotor parameters. There were no differences between the groups on day 1, but the treated group showed significantly lower scores for general stiffness and painful rise on day 28 and also the total scores were lower. The scores for specific lameness and exercise intolerance did not differ between the groups.

On day 28, when one group had been on treatment for 4 weeks and the other group for 3 weeks, there was a significant reduction of the scores for all locomotor parameters. The palatability of the suspension was good, 32 dogs accepted the food without difficulties, 5 dogs accepted the product with some difficulties, while one dog refused to take the product.

One dog in the placebo group died during the first phase, the dog was not autopsied as the death was unrelated to treatment. Four dogs showed mild gastro-intestinal symptoms (diarrhoea and vomiting). No haematological or blood chemical changes occurred during the treatment period. Metacam oral suspension appeared to be well tolerated and the scores for the locomotor parameters were reduced during the treatment period. However, the last clinical examination was performed on day 28, the last day of treatment. The risk for relapses therefore cannot be assessed.

Metacam 0.5 mg/ml oral suspension for dogs

For Metacam 0.5 mg/ml oral suspension, reference was made to the efficacy documentation submitted and approved for Metacam 1.5 mg/ml oral suspension.

Clinical Studies (cats)

Metacam 0.5 mg/ml oral suspension for cats

A GCP-compliant study was carried out to determine the efficacy of 0.1 mg/kg/day meloxicam in relieving the arthritic pain of cats produced in a urate-induced arthritis model using Metacam 1.5 mg/ml oral suspension. The study was of randomised, blinded, placebo controlled, single cross over design. There were clear differences between test and control groups in some parameters.

A further GCP-compliant study was carried out, again using Metacam 1.5 mg/ml oral suspension. The study was of randomised, blinded, placebo controlled, four-way cross over design and used a protocol similar to the previous (pilot) study. Three different doses were used, all lower than the 0.1 mg/kg found to be efficacious in the pilot study. A significant effect was recorded. The model used was regarded as sensitive as the challenge is given after administration of the test compound (preventive effect) and a sufficient number of animals allowed the effect to reach statistical significance. No differences in effect were found between doses which is not surprising as the differences between the doses were small. No kinetic data were recorded in this study but it seems likely that the exposure from 0.05 and 0.075 mg/kg overlap. The objective with the dose finding studies was to find the lowest possible dose where any effect could be recorded (LOED, lowest observed effective dose). This dose using this model was found to be 0.05 mg/kg/day.

A published non – GCP trial to evaluate the clinical efficacy and palatability of meloxicam in cats with painful locomotor disorders was presented. The study was a non-blinded randomised parallel design study. The groups were of different sizes as 43 cats were allocated to the test group and 26 to the control group. The animals were recruited from 14 veterinary practices.

General demeanour, food intake, weight bearing at rest, lameness, local inflammation and pain on palpation. In addition, an overall clinical assessment of therapeutic efficacy was performed. Assessment was made using four step scales on days 2 and 6.

Both groups performed equally well. There were no statistically significant differences between groups for any of the investigated parameters. There was an overall significant improvement from day 1-6 in weight bearing, reduction in lameness, reduction in pain on palpation and reduction in inflammation of the affected area was seen in both groups. There was also a significant improvement from day 1-2 in weight bearing and reduction in pain on palpation in meloxicam cats, and decrease in lameness in ketoprofen cats. The parameter overall assessment of efficacy improved significantly from day 2 –6 in both treatment groups.

The palatability was regarded as good in 74 % of the cats receiving meloxicam and 20 % of the cats receiving ketoprofen. In the meloxicam group one cat vomited, one showed intermittent slight retching, two showed a decrease in feed intake during the treatment period (the clinical signs of one of these worsened despite treatment). In the ketoprofen group one cat vomited on one occasion.

As no placebo group was included, the drug independent cure rate in this study is not known. The level of side effects seems to be comparable to the approximately 10 % known from clinical trials in dogs.

Clinical efficacy of meloxicam (Metacam 0.5 mg/ml oral suspension) in cats with painful chronic locomotor disorder

A GCP-compliant, double-blinded, randomised, placebo-controlled multi-centre clinical field study was performed to test superiority of meloxicam in comparison with placebo. In case of animals not showing any clinical improvement after 7 or 14 days of treatment according to the clinical sum score, the treatment could be stopped and continued with open labelled meloxicam.

The test formulation was Metacam 0.5 mg/ml oral suspension or placebo. Metacam was given orally at an initial dose of 0.1 mg/kg, followed by 0.05 mg/kg once daily. Placebo was given orally once daily. The treatment was given for up to 28 days. The majority of cats were Domestic Short Hair and on average 10.8 years of age. At study inclusion the locomotor disorder had been already present for an average of 412 days. The most frequent diagnoses were osteoarthritis and spondylosis.

Examination of the locomotive system was performed by the veterinarian. Assessment of mobility, posture, gait and palpatory pain were eventually added up to a Clinical Sum Score (CSS). In addition, blood sampling on days 0 and 28 and serum biochemical analysis was performed in one third of the animals. Appropriate inclusion and exclusion criteria were used.

On day 0 an initial dose of 0.2 ml/kg, equivalent to 0.1 mg meloxicam/kg body weight, was administered by the veterinarian. The maintenance dose of 0.1 ml/kg, equivalent to 0.05 mg meloxicam/kg body weight, was administered by the animal owner from day 1. The product was administered either with a syringe (provided) directly into the cat's mouth, or with a small amount of feed to be eaten immediately. The owner treated the cat daily, and brought the cat to the investigator for examination and blood sampling at days 7, 14 and 28 of the study. Any permissible concomitant treatment was documented and classified on the Case Report Form.

The treatment groups were compared regarding the primary parameter (AUC_{CSS}) using Wilcoxon Mann-Whitney test due to significant deviations from the normal distribution. The group size allowed a difference between treatment groups of at least 24.5 regarding AUC_{CSS} corresponding to a decrease of the sum score by 1.0 score point to be detected. The marketing authorisation holder considered this level to be clinically relevant. The individual scores included in the CSS were statistically evaluated using the same methods as for the CSS.
Secondary parameters, such as feed intake, temperament and social behaviour, as well as palatability, were tested on differences using the Wilcoxon Mann-Whitney test.

The data set consists of the results of 125 animals from 29 investigators. Five animals were excluded from the statistical evaluation due to various reasons. An additional 25 animals (meloxicam 14, placebo 11) switched to open labelled meloxicam treatment after day 7 or day 14. The "subpopulation" consists of cats that were evaluated and treated blinded until day 28 (meloxicam 46, placebo 48). The "entire population" consists of the subpopulation plus the 25 animals that switched to open labelled meloxicam treatment and one animal with premature study termination and withdrawal (meloxicam 60, placebo 60). For these 26 animals, the last scores for mobility, posture, gait and palpatory pain generated before switching to open labelled meloxicam treatment or before withdrawal were also used for the following prescheduled visits, allowing AUC calculation for all animals from 0 to 28 days (entire population analysis).

The CSS decreased continuously over the study period in both treatment groups and to a greater extent in the meloxicam group. Tests on differences between groups revealed no significant difference at the defined significance level of $p \leq 0.05$ for the AUC. There was a significant difference at $p \leq 0.1$ but only over the treatment period from day 0 to day 14 and only in the subpopulation.

The average mobility, posture, gait and palpatory pain scores decreased continuously over the study period in both treatment groups with no significant differences between groups. When analysing the mean change of AUC from baseline for palpatory pain it was found that this area was larger in the meloxicam group compared with the placebo group. The differences in AUC based on changes from

baseline, over the treatment periods 0 – 14 days and 0 – 28 days, were significant at the $p \leq 0.05$ level for the entire population as well as the subgroup. The difference in score was most prominent at Day 7. However, there were minor differences in mean score at the respective time points (mean scores were 2.8, 2.2, 1.9 and 1.6 versus 2.7, 2.4, 2.1 and 1.7 for meloxicam and placebo at Day 0, 7, 14 and 28 respectively (subpopulation data).

The mean feed intake, social behaviour and temperament score decreased over the study period, approximately to the same extent in both groups. There was no significant difference in AUC between groups, at the $p \leq 0.05$ level.

For the temperament score, the mean change of AUC from baseline was larger in the meloxicam group compared with the placebo group and the differences were significant at the $p \leq 0.05$ level for the entire population as well as the subpopulation. The mean scores were 2.2, 1.5, 1.3 and 1.2 versus 2.1, 1.9, 1.7 and 1.5 for meloxicam and placebo at Day 7, 14 and 28 respectively (subpopulation data). The mean rectal temperature was comparable in both treatment groups during the study period. No clinically relevant differences pre- and post treatment values of serum biochemical parameters were noted except in one case (see below). The palatability was found to be excellent in approximately 50 % of the cases and less than 10 % were reluctant. Data were similar for both groups.

The marketing authorisation holder discussed the choice of endpoint and justified why the primary endpoint “clinical sum score” was less appropriate for the assessment of locomotor pain in cats. Cats suppress visible signs of chronic musculoskeletal pain unless they are stimulated to show this pain and thus palpatory pain is an appropriate parameter. Other measures (posture, gait, mobility) are less pain-specific, and are also extremely difficult to assess in a clinical environment. The marketing authorisation holder also discussed the possibility of introducing bias in this case.

Metacam 0.5 mg/ml oral suspension was considered highly palatable in most cases.

Adverse events were reported for 8 cats (meloxicam 5, placebo 3). In the meloxicam treated animals the following adverse events were reported. In one cat vomiting, polyurodypsia, increased serum urea and creatinine were reported . Another cat was reported with vomiting, 5 weeks after treatment start, the animal was euthanized due to continued vomiting. This cat was diagnosed with abdominal mass, which was histologically determined as adenocarcinoma. Vomiting and gastro-oesophageal reflux was reported in another case, with a start of the adverse event 10 days after treatment start. The symptoms sustained for 5 days and stopped in spite of continued treatment over 28 days. A single episode of vomiting was reported for 2 cases, which recovered within 10 minutes and one of them had also a short episode of diarrhoea on the last treatment day (Day 28). From the placebo treated animal the adverse events reports included one cat with apathy, one cat with progressive paralysis of hind limbs and one cat with mild polydipsia and elevated serum creatinine.

The marketing authorisation holder concluded that the oral administration of Metacam 0.5 mg/ml oral suspension, at an initial single dose of 0.1 mg/kg followed by 0.05 mg/kg once daily, is safe and efficacious for the alleviation of inflammation and pain in chronic musculo-skeletal disorders of cats.

Risk-Benefit Assessment for Metacam 1.5 mg/ml for dogs and Metacam 0.5 mg/ml for dogs

Data from toxicological studies were assessed in the Metacam 5 mg/ml Solution for Injection application. The safety data included in this extension application covered primarily user safety and ecotoxicity. There were no remarkable findings regarding clinical signs, changes in body weight, haematology, clinical chemistry, and urinalysis. There were also no reported adverse effects revealed at (thorough) autopsy, including a lack of findings at the site of application. Thus, it appears that meloxicam in topical solution was without local as well as systemic effects in this study. The dermal absorption of meloxicam was 5-30% of that absorbed orally.

Safety was not documented in pregnant and lactating females and a relevant warning for use in pregnant and lactating bitches was included in the SPC. As safety was not documented in puppies and

very few young dogs were included in the safety studies Metacam is contraindicated in dogs less than 6 weeks of age.

Metacam 1.5 mg/ml oral suspension is well documented in a number of studies of sufficient size for treatment of acute and chronic inflammatory and painful processes in muscles and skeleton in the dog with the suggested dose regimen. The duration of the treatment period is not given. It may be concluded from the submitted studies that treatment can continue safely for 28 days. It was requested that in order to reduce the risk for severe adverse reactions, the treatment period should be restricted to 28 days. The marketing authorisation holder pointed to the available data on pharmacovigilance that there was no evidence of an increased risk after 28 days of treatment and that a limit in the treatment period was not included in the present national authorisations. Furthermore, a treatment period beyond 28 days seems to be justified in chronic locomotor disease conditions and the argumentation is accepted. Likewise, there seems to be little reason to provide for a minimum treatment period as the effect is reached quite soon after initiation and the treatment in any case is mostly symptomatic.

The risk-benefit of Metacam 0.5 mg/ml oral suspension for Dogs was also assessed. The documentation provided was considered acceptable with regard to the quality, safety and efficacy of the product.

Risk-benefit assessment of Metacam 0.5mg/ml oral suspension for cats

With 0.05 mg/kg bodyweight a dose corresponding to the lowest effective dose rather than the optimum dose has been identified. As the parameters used for efficacy assessment in the pivotal clinical field trial had not been established in a previous exploratory study, exploratory elements have been introduced into the confirmatory trial, and a re-assessment of the results has been performed *a posteriori*.

Slight but statistically significant differences have been detected between the treatment and the control group, which may in part be explained by the fact that cats suffering from very severe disorders had not been included. However, the CVMP considers the risk/benefit of Metacam 0.5 mg/ml oral suspension for long term treatment in cats at a dose of 0.05 mg/kg bw/day to be positive.

With experimental and clinical studies the marketing authorisation holder has identified a dose scale which ranges from a low effect dose to more potent doses. The 0.05 mg dose proved to be the lowest effective dose in the experimental dose finding studies and was selected. Considering the principal difficulties encountered with such studies in cats, this dose exhibited positive effects. There was a uniform trend towards better results in the treatment group with respect to other efficacy parameters.

Under safety aspects, 0.05 mg/kg appears acceptable, as the tolerance studies revealed only slight side effects in cats treated for a prolonged period with this dose. The information submitted by the marketing authorisation holder provided evidence that Metacam 0.5 mg/ml oral suspension at a dose of 0.05 mg/kg bodyweight or even lower doses was appropriate for long-term pain management in cats in practice.

VI METACAM 15 MG/ML ORAL SUSPENSION FOR HORSES

Metacam 15 mg/ml oral suspension for horses is intended for the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders.

Quality Assessment
Composition

Qualitative Composition	Quantitative composition mg/ml suspension	Reference to analytical quality
Meloxicam	15.00	BP + additional in house test
Other excipients	to 100 per cent	EP or in house test

Container
Metacam 15 mg/ml oral suspension is packed in a plastic screw necked bottle with dropper and screw closure having an original tamper-proof child resistant closure and a 24 ml oral syringe with an integrated adapter and with a “kg/body weight“ graduation. The pack size is 100 ml.

Clinical Trial Formulae
Clinical trials have been performed with the composition proposed for marketing. In addition clinical trials have been performed with a different formulation.

Development Pharmaceutics
Meloxicam is sufficiently soluble in an alkaline medium to form a solution. A meloxicam solution is unstable and has a very bitter taste and therefore an aqueous suspension of meloxicam was developed. Sodium benzoate is used as preservative. The chosen concentration preserves the suspension in accordance with the requirements of USP XXII and of Ph. Eur. This is also shown for the 75% concentration.

The manufacturing process development was described in detail. In-vitro comparison of the two formulations of the oral suspension has been performed. The differences are considered to be of no significance. Documentation was provided on the capability of the proposed dissolution testing procedure to ensure adequate discrimination between batches of acceptable and unacceptable in-vivo performance (to ensure consistency in the bioavailability).

The active substance particle size is the critical factor for the in-vivo performance of the product. Therefore, the company has manufactured 3 batches of active substance with different particle size distribution, and the dissolution profiles for the three products have been compared, demonstrating the satisfactory discriminating power of the dissolution method. The dissolution test will not be included in the FPS.

One of the batches used for the in-vitro bioequivalence study has also been used during the pharmacokinetic study, so the in-vitro/in-vivo correlation of the product is known. Growth of particles (recrystallisation) during storage has not been observed. The formulations can be considered to be in-vitro equivalent to each other.

The graduated measuring syringe has been tested for dosing accuracy, for body weights from 25 to 600 kg (50-1200 lb). The data show that the requirements of the Ph.Eur. for dosing accuracy are fulfilled.

Manufacturing chain

The active substance manufacturer is Bidachem SpA, Strada Statale 11 (Pad.Sup.) 8, 24040 Fornovo San Giovanni (BG), Italy. Boehringer Ingelheim Vetmedica Inc. 15& Oak, Elwood, Kansas 66024 USA is manufacturer of the product, which includes control of the starting material, manufacture of the finished product, filling and closing, analytical controls and finished product shipping.

Boehringer Ingelheim Vetmedica GmbH, Binger Str. 173, 55216 Ingelheim am Rhein, Germany is responsible for final control and is in charge of batch release in the EEA.

Manufacturing Formula and Batch Size

The manufacturing formula was presented for the two alternative batch sizes, 500 kg and 1000 kg.

Manufacturing process

The manufacturing process was described in a flow diagram. In-process controls performed are appearance/odour, particle size, relative density and pH. In addition, after filling into the final containers the filling volumes are tested. The in-process specifications were presented.

Validation of Manufacturing Process

Three full scale batches of 500 kg each were prepared at Boehringer Ingelheim Vetmedica USA. Samples were collected during the process and analysed for chemical, physical and microbial properties. All process parameters have been studied at the originator site BIKG and the critical variables identified.

Tested parameters have been assay (meloxicam, sodium benzoate), viscosity, pH, particles, net content and microbial contamination. All tested samples, with one exception were within the specification limits One bottle collected at the end of fill was out of specification (106%). 10 samples were retested with acceptable results.

The validation of the manufacturing process was considered acceptable.

Active ingredients listed in a Pharmacopoeia.

The quality of the active substance meloxicam conforms with BP with additional tests on particle size and residual solvents.

Physico-Chemical Characteristics liable to affect bioavailability

The in vitro dissolution behaviour of the suspensions used during the development has been studied and it can be concluded that the formulations are in vitro equivalent to each other.

Quality control during manufacture

Specifications are included for the starting materials, auxiliaries and solvents in the dossier. The quality control during manufacture of meloxicam has been previously assessed and approved for the previously authorised Metacam presentations.

Impurities

Two additional statement were provided: “Possible impurity IVa in Meloxicam drug substance” and “Possible impurity IVb in Meloxicam drug substance”. These statements describe the correct structural fomulae for the two mentioned impurities, discovered with new NMR techniques. These possible impurities occur either as a result of the synthetic route or by degradation.

Batch analysis

Batch analysis data from three industrial scale batches were presented. These batches were manufactured in February and in April 2000 at Bidachem S.p.A. and milled at Boehringer Ingelheim Pharma KG. All results complied with the presented specifications.

In addition batch analysis results from three milled meloxicam batches produced at Bidachem and results from three batches produced at the previous manufacturing site (BI Pharma KG Biberach) are presented. All results comply with the specifications.

Batch analysis results for the reference substance (identity, purity and assay) were presented. It was noted that the reference substance in the BP has been provided to BP from Boehringer Ingelheim.

Excipients

The excipients are tested and evaluated according to the current Ph. Eur. Honey aroma is not described in Ph. Eur. or in any other pharmacopoeia of a Member State. The submitted testing specifications were considered acceptable.

Packaging

The plastic screw-necked bottle, dropper and child resistant screw closure (inner cap) are all tested for identity and for dimensions/appearance. The barrel, plunger and sealing ring are tested for identity.

During development the graduated measuring syringe has been tested for dosing accuracy, for body weights from 25 to 600 kg and found to comply with Ph. Eur. "Liquida peroralia". The specification for the oral syringe was expanded to include a reference to appearance (e.g. clarity and frequency of markings) and a test for accuracy of markings. A clear drawing of the oral syringe and a sample of the syringe were provided.
The packaging components comply with the relevant requirements.

TESTS ON THE FINISHED PRODUCT
Product Specification and Routine Tests:

Table 2: Release and shelf- life specifications for Metacam 15 mg/ml oral suspension for horses.

Test attribute	**Test method**
Appearance, odour	
Meloxicam, identity	HPLC
Meloxicam, assay	HPLC
Sodium benzoate, identity	HPLC
Sodium benzoate, assay	HPLC
Meloxicam, purity test	HPLC
Microbial contamination	Ph. Eur.
Particle size	Microscopy
Redispersibility	Shaking
Viscosity	Rotational viscometer
Volume of contents	Weighing, in process
pH	
Relative density	Pyknometer alt. Paar density meter

Tests procedure for identification and quantitative determination for the active substance(s)

HPLC is used for identity and for assay of meloxicam and sodium benzoate. Both are identified against standards and for meloxicam there is an additional PDA spectrum identity control against standard. An impurity test is performed and the microbial purity is tested. In addition the oral suspension is tested for viscosity, pH, particle size and relative density.
Analytical validation of methods and comments on the choice of routine tests and standards
The HPLC method used for identification, assay of sodium benzoate, meloxicam and for the determination of the decomposition of active ingredient has been validated. The assay methods have been validated with respect to specificity, linearity, accuracy, intermediate precision and robustness. Validation parameter for identity is specificity (meloxicam, 2-amino-5-methylthiazole, sodium benzoate). Validation parameters performed for the degradation determination method are specificity, quantification limit, linearity, accuracy, repeatability and robustness.

The method has been revised with respect to sample preparation. Stored samples which were tested with the original method have been re-analysed with the revised method and the validation considered acceptable.

Batch analyses

Certificate of analysis for three batches (500 kg) of Metacam oral suspension for horses were presented. The specification valid at that time did not include PDA spectrum (reference to standard) for identity of meloxicam nor relative density. All results were within the stated limits and the specifications for the finished product were considered acceptable.

The impact of low temperatures and fluctuations in the temperature (e. g. freeze/thaw) have upon the product are to be investigated, particularly as the product is likely to be stored in stables where there will be no temperature control. The marketing authorisation holder has committed to carry out a thorough investigation of the effects of low temperature and fluctuations in the temperature on the product. The data has been subsequentially submitted and has been considered acceptable.

Stability Tests on the Active Substance(s)

Stability tests on the active substance were presented. Results from storage of three jet-milled batches of the substance for up to 60 months at 25°C/60%RH / 30°C/70%RH and for up to 6 months at 40°C/70%RH were available. The batches were produced by Bidachem and milled at BI Pharma KG Biberach (name changed from Dr Karl Thomae GmbH in January 1998). Tested parameters: appearance, identity, IR-spectrum, clarity of solution, purity (HPLC), water content, assay (HPLC) and particle size. No relevant changes were observed. The milling process seems to have no influence on the stability of the substance. The proposed retest period is 5 years, stored in the tested packaging material; this is considered acceptable.

Stability Tests on the Finished Product

Product Specification and Routine Tests for shelf life:

Parameters studied are appearance, odour, pH, re-dispersibility, particle size, viscosity, loss in mass (only one batch), microbiological characteristics (microbial contamination, antimicrobial preservative effectiveness test or efficacy of antimicrobial preservation), assay and degradation of meloxicam, assay of sodium benzoate and packaging characteristics (appearance and function). The methods used are in accordance with the testing specification for the finished product.

Stability Tests
One stability test report includes stability data from long term storage and from storage at accelerated conditions for one batch produced at BI Pharma KG, Biberach. Two testing specifications were used. Only results from the current valid specifications are included. This report is presented as supporting data to the main stability study.

The main stability study is performed with three 500 kg batches manufactured by BI Vetmedica, Elwood Kansas. The batches have been stored for up to 12 months at 25°C/60%RH, at 30°C/70%RH and at 40°C/70%RH. Subsequentially, he shelf life has been extended to 3 years.

The results from the tested parameters appearance, odour, resuspendibility, packaging material, pH, particle size and viscosity were all within the specifications. The pH remained within ± 0.3% units of that determined at release. The particle size remained unchanged. The viscosity varied during the study although all results were within the specification. No loss of mass was determined.

The meloxicam content was between 95 to 101% under all studied conditions. The degradation was minimal, with no 2-amino-5-methylthiazole detected and at most 0.02 % of degradation products.

The sodium benzoate content decreased depending on storage time and temperature. The results were however within the shelf-life limits.

Antimicrobial preservative effectiveness test were performed with samples after storage up to 12 months at 25°C, 60 RH %. The samples met the USP and the Ph. Eur. requirements.

In-use stability

Three batches have been stored at ambient warehouse temperature with uncontrolled humidity. Samples of 20 ml were collected at study initiation and after 1 and 3 and 6 months of storage. The opened bottles were closed and stored at 25°C/60% RH.

Amongst the parameters tested were appearance, odour, pH, resuspendability, particle size, viscosity, degradation of meloxicam, assay of meloxicam, assay of sodium benzoate, efficacy of antimicrobial preservation, microbial contamination and packaging material. The validation of the test procedures was satisfactory. No relevant changes in the physico-chemical characteristics were observed after 6 months. The pH and sodium benzoate are unchanged.

Photostability

A light exposure test was performed in a very similar formulation in the polyethylene bottles intended for marketing and for comparison in colourless glass flasks (not intended for marketing). Light exposure 22 hours Xenon light. In addition the containers were wrapped in aluminium foil. Parameters tested were: appearance, odour, pH, redispersibility, particle size, viscosity, degradation, assay of meloxicam and of sodium benzoate. Degradation was only observed in the un-wrapped glass flasks. No other relevant changes were observed. The proposed “no special precautions for storage” is considered acceptable.

Safety Assessment

User Safety

Previously assessed studies showed that meloxicam is neither a dermal nor an ocular irritant. The person administering the drug is therefore not exposed to any risk. Consequently no special precautions are deemed necessary.
Conclusion including the risk management proposals

Meloxicam 15 mg/ml oral suspension appears to be safe when used as proposed and does not pose any risk for the person administering the product. The SPC text 'Individuals sensitive to NSAIDs should avoid contact with the product' is considered sufficient.

Ecotoxicity - Phase I Assessment

The product is intended for the treatment of individual animals. No herd treatment will occur and therefore further ecotoxicological assessment is not necessary. This is in accordance with the VICH Guideline (GL6, CVMP/VIVH/592/98 –Final).

Conclusion on Part III.A.

Metacam oral suspension is considered safe when used as recommended. The marketing authorisation holder's proposal concerning ecotoxicity is acceptable and no special warnings for the person administering the product are necessary.

Residue studies

A study comparing the pharmacokinetics of meloxicam after intravenous an oral administration in horses was also included in the application submitted for the extension of the MRLs for meloxicam to include the target species horse.

Residue depletion study in horses

A depletion study of tissue residues following repeated oral administration of meloxicam in horses was submitted.

Test conditions: Twelve horses (6 male and 6 female weighing 470-542 kg prior to dosing) were randomly assigned to 3 groups of 4 animals (2 male and 2 female). Each group received an oral nominal dose of 0.6 mg meloxicam/kg bodyweight (Metacam 15 mg/ml oral suspension) once daily for 14 consecutive days. The doses were administered orally in a small portion of each horses´ morning food ration (except for one animal which received the doses in the afternoon). After the final administration one group was sacrificed at 12, 24 and 48 hours post last dose. Samples of liver, kidneys and muscle from the hind quarter were analysed for residues of meloxicam using a validated HPLC procedure.

Results: The actual daily doses administered to each horse were in the range of 0.600-0.605 mg/kg bodyweight. The concentrations of meloxicam measured in tissues are presented in table 1.

Table 1. Concentrations of meloxicam in the tissues of horses treated orally once daily with 0.6 mg meloxicam/kg b.w. for 14 consecutive days. Results for mean and individual values in µg/kg.

Withdrawal time (h)	**Liver**	**Kidney**	**Muscle**
12	98.3	1350	20.7
	146	814	<LOQ
	126	1740	35.1
	90.4	1200	17.1
Mean	**115**	**1280**	**18.2**
24	69.1	621	<LOQ
	70.4	454	ND
	47.7	450	<LOQ
	45.4	553	<LOQ
Mean	**58.2**	**520**	**<LOQ**
48	<LOQ	43.9	ND
	<LOQ	76.3	ND
	<LOQ	74.8	ND
	<LOQ	30.2	ND
Mean	**<LOQ**	**56.3**	**ND**

LOQ = Limit of quantification (20 µg/kg for liver and 10 µg/kg for muscle)
ND = below limit of detection (3.3 µg/kg for muscle)

This residue depletion study was performed according to the requirements in Volume 8 of the Rules Governing Medicinal Products in the European Community and submitted as part of the application for the establishment of MRLs for horses.

Maximum Residue Limits (MRLs)

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	

The excipients included in Metacam 15 mg/ml oral suspension (according to the qualitative and quantitative composition) were therefore either included in Annex II of Council Regulation (EEC) No 2377/90 or out of scope of this regulation and do not present any risk for the consumer.

Withdrawal period

A withdrawal period of 3 days was proposed for horses after administration of Metacam 15 mg/ml oral suspension at the recommended dosage. This is based on the residue depletion study presented, the MRLs established for horse tissues and a statistical evaluation of the residues in kidney using the approach recommended by the CVMP (EMEA/CVMP/036/95).

The residue depletion study was performed according to guidelines and is relevant for the determination of the withdrawal period. In muscle the concentrations of meloxicam were <LOQ 24 hours after the last administration in all horses and in liver the concentrations of meloxicam were <LOQ 48 hours after the last dosing in all horses. The highest concentrations of meloxicam were measured in kidney. Forty-eight hours after the last administration meloxicam concentrations were below the MRL of 65 µg/kg in two of the four horses while the concentrations in kidney of the other two horses were above the MRL. Using the statistical approach recommended by the CVMP (EMEA/CVMP/036/95) on the residue concentrations in the kidney, based on the MRL of 65 µg/kg, results in a withdrawal period of 58.4 hours. Muscle and liver will not affect this withdrawal period as meloxicam residues from all horses were below the MRL for muscle and liver at 24 and 48 hours, respectively.

The samples collected in the residue depletion study were analysed by a fully evaluated method. However, the samples were stored for 5 months at –20° before analysis. The marketing authorisation holder made reference to two earlier submitted studies, VU-01109 and VU-01108. In the first of these studies meloxicam containing cattle tissue samples were stored at –20 C for one month. Meloxicam showed acceptable stability as >96% of the original value was found at analysis after one month. The stability of meloxicam was demonstrated also in the second study. Cattle tissue samples spiked with meloxicam were stored at –10 C for 9 months. The concentrations of meloxicam on Day 0 were 0.324 µg/g and 0.647 µg/g in muscle and liver, respectively. The corresponding values after 9 months were 0.388 µg/g and 0.719 µg/g.

Routine Analytical Method for the Detection of Residues

A routine analytical method for the determination of meloxicam in horse tissues was based on HPLC using UV detection and presented in the ISO 78/2 format. The method was based on the fully validated method for bovine tissues, met 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.

Clinical Assessment

Pharmacodynamics

A number of studies performed in horses were submitted.

Pharmacodynamics and pharmacokinetics of meloxicam in the horse. Brit.vet.J. 1991, 147, 97

The well-established carrageenan-sponge model was used. This technique allows sampling of inflammatory exudate for analysis of drug and inflammatory indicators. Six ponies carrying subcutaneous carrageenan sponges were injected intravenously with 0.6 mg/kg b.w. of meloxicam. Plasma samples and inflammatory exudate were collected at predetermined intervals. The surface skin temperature of the inflamed area was lower in the treated group than in the placebo group, but the difference did not reach statistical significance.
The number of leucocytes in the exudate and the exudate protein concentration increased with time, but did not differ significantly from the placebo group. The serum TXB_2 concentration in plasma was significantly lower in the treated group at 4, 8, and 12 hours after treatment. Treatment reduced the exudate concentration of TXB_2 significantly for up to 12 hours, of 6 keto PGF_{1a} for up to 8 hours, and of bicyclic PGE_2 for up to 8 hours.

LDH and acid phosphatase occurred in the exudate, but there were no differences between the groups. The concentration of meloxicam in plasma was compared with the concentration in exudate.

The results are shown in the table below:

b) Time h	Plasma conc. ng/ml	Exudate conc. ng/ml	Exudate: plasma ratio
4	896 ±117	900 ±136	1.04 ± 0.36
8	393 ± 43	517 ± 58	1.36 ±0.16
12	107 ± 58	347 ± 78	2.96 ± 0.96
24	0	48 ± 30	-

Pharmacokinetics

1) Dose titration and pharmacokinetic study with Metacam in the horse.

The aim of this study was to determine the dose-effect relationship and the pharmacokinetics of Metacam in the horse. The Freund's complete adjuvant carpitis model was used and five different intravenous single doses were tested in order to find a suitable dose for testing Metacam in clinical trials. The study was of sequential cross-over design and a PK/PD analysis was performed simultaneously. The reason for choosing the sequential cross-over design was that higher doses of Metacam would probably had been necessary for significant drug effects in a study of the common

parallel dose design due to individual variations in response, and the small number of animals used. The arguments seem reasonable.

Six horses were included in the study. Arthritis was induced by injection of Freund's complete adjuvant into the right carpal joint. The horses were randomly allocated to treatment with Metacam at the doses 0, 0.25, 0.5, 1.0 and 2.0 mg/kg b.w. The doses were given as single intravenous injections. The interval between treatments was one week.

Freund's complete adjuvant usually induces lameness with a duration of several weeks, but two horses had to be re-injected in order to maintain lameness.

All horses had been treated with all five doses of Metacam at the end of the study. The first Metacam treatment was given 7 or 8 days after induction of arthritis and re-injection with Freund's adjuvant was given 48 hours after Metacam treatment. Stride length and lameness score were considered as the primary parameters. Lameness was assessed at rest (weight bearing), at walk and at trot. Lameness was assessed using a scale graded to 20. Rectal temperature, circumference of the right carpal joint, local skin temperature, rest angle flexion and maximal forced carpal flexion of the right forelimb were secondary parameters.

Blood was collected at predetermined time points after each injection of Metacam for analysis of the plasma concentration. A fully validated analytical HPLC method with UV detection was used for the analysis. The limit of quantification was 10 ng/ml and the limit of detection was 4 ng/ml. The analysis of the effect of the different doses of Metacam on stride length and lameness score was performed using the following statistical methods in succession;

- a multifactor ANOVA test to show the existence of a dose effect
- a multiple regression analysis to show the existence of a dose-effect relationship
- a non-linear regression analysis to determine the parameters of an Emax pharmacodynamic model with the dose or the AUC as independent variable. For these analyses the data from all horses were pooled.

The methods used in the pharmacokinetic analysis and the PK/PD modelling are described in detail and reference is made to relevant publications which are attached to the report. The results for the primary parameters were given in tables and graphs. The results obtained after 4, 6 and 8 hours were statistically analysed. The ANOVA analysis showed that none of the tested factors (dose, horse, period) had significant effects on stride length, but there was indication of a dose effect when the Duncan test was applied.

The ANOVA test indicated a significant dose effect on lameness score, but no significant horse or period effect. When the Duncan test was applied, the dose 0.25 mg/kg b.w. showed significant effect over placebo, but a statistically lower performance than the higher doses. There were no significant differences between the three highest doses (0.5, 1.0 and 2.0 mg/kg b.w.).

In contrast to the ANOVA test, the multiple regression analysis evidenced a significant dose-effect relationship on stride length, horse and period had no effect. The multiple regression analysis also showed a highly significant effect on lameness score, but no effect for horse and period.

The Emax model was used for calculation of relevant pharmacodynamic parameters such as Eo, Emax and ED50. For the time points 4, 6 and 8 hours after Metacam administration the overall ED50 for stride length was 0.120 mg/kg b.w. and the Emax was 11.5%. The overall ED50 for lameness score was 0.265 mg/kg b.w. The overall Emax was 9.16 lameness score units. It seems logical that ED50 was higher for lameness score than for stride length as lameness score was recorded also at trot and stride length only at walk. Trotting obviously triggers more painful stimuli than walking.

The overall ED60, ED70 and ED80 for lameness score were 0.397, 0.617 and 1.06 mg/kg b.w. The EC50 for lameness was calculated to be 146 ng/ml. The model was further described and discussed in

a separate report (Expert statement on the selection of an appropriate dosage regimen for Metacam in horses.

The carpitis model was considered as a very severe inflammatory condition. The dose proposed for clinical use, taking also the risk for adverse reactions into consideration, was 0.6 mg/kg b.w., i.e.ED70 of the carpitis model. The calculations showed that increasing the dose from 0.6 to 1,0 mg/kg b.w. would only marginally increase efficacy. The secondary parameters were not compared statistically.
The mean plasma clearance of meloxicam was low 0.081 l/kg. The volume of distribution was 0.23 l/kg which is similar to the volume of the extracellular water space. The elimination half-life was 5.15 h. No adverse reactions occurred.

Bioavailability

2) Intravenous and oral pharmacokinetic study with meloxicam in the horse.

The study was discussed in III. B. 2. 1. The absorption of meloxicam was delayed when administered together with food, but the total bioavailability was not changed. Meloxicam did not accumulate in plasma after daily treatment with 0.6 mg/kg b.w. for 14 days.

Protein binding

Protein binding of (^{14}C) UH-AC 62XX in horse and domestic pig plasma

Protein binding was determined using ultrafiltration and ultracentrifugation. The results of both methods were similar, 96-98% binding. The binding rate was similar over a wide range of concentrations.

Tolerance in the target species

Metacam 1.5% oral suspension: Target animal safety studies in horses.

The aim of the study was to determine the safety of Metacam in horses after oral administration of up to ten times (10X) the recommended dose for up to three times (3X) the recommended treatment period. However, when the adverse reactions after five times (5X) the recommended dose became evident, the highest dose group was never treated.

Twenty-eight horses, 2-14 years old and weighing from 370 to 518 kg were randomly allocated to four equal groups. The groups were treated once daily with the following doses of Metacam: 0, 1X, 3X and 5X the recommended dose (0.6 mg/kg) for 42 days. Treatment was given by a syringe and a tube directly into the mouth.

Clinical observations were performed daily and blood was collected at predetermined intervals for haematological and clinical chemistry examinations. All animals were necropsied at the end of the study. The study was blinded, meaning that the persons responsible for clinical examinations and necropsies were unaware of the treatment.

The conclusion of the study was that 3X and 5X the recommended dose for 3 times the recommended period, induced lesions of the mucosa of the gastrointestinal tract and in the kidneys, that are typical for that class of compound, while the recommended dose appeared to be well tolerated. Safety was not documented in pregnant and lactating animals nor in foals.

The dose was determined using an established carpitis model, the primary parameters were stride length and lameness at trot. The dose 0.25 mg/kg b.w. was found to reduce lameness significantly, but significantly better effects were obtained after higher doses. Using PK/PD modelling, a dose of 0.6 mg/kg b.w. was proposed for the clinical trials. The carpitis model was considered to be a very severe clinical challenge and the proposed dose was equal to ED70 of the model. Higher doses were found to be only marginally better. The proposed dose is considered acceptable when the risk for adverse reactions is also taken into consideration and the dose was further confirmed in the efficacy studies.

The results of the safety study show that the therapeutic index of meloxicam in the horse is narrow. Treatment with the recommended dose for 3 times the recommended period of time did not induce any adverse reactions. Higher doses, 3X and 5X the recommended dose for 3 times the recommended period, induced serious reactions such as severe weight loss, oedema, ulcerations of the mucosa of the gastrointestinal tract and papillary necrosis of the kidney. The lesions are characteristic for this class of compound.

Intravenous bolus doses up to 2 mg/kg bodyweight were well tolerated in the dose finding study.

The age limit for foals in the SPC was justified by reference to a published report by Kietzman and Löscher (Berl. Münch. Tierärtzl. Wschr. 103, 277-282, 1990) describing the differences in drug disposition and drug elimination between very young and adult animals. The age dependent differences are considered to be due to differences in the secretion of gastric juice, extracellular space, fatty tissue as proportion of body weight, maturation of enzyme systems and renal function. According to this publication, pharmacokinetic differences should be especially considered within the first 3 to 4 weeks of age. In order to add an additional safety span, the marketing authorisation holder proposed to use Metacam only in foals older than 6 weeks and this was considered appropriate.

Clinical Studies

1) Clinical efficacy of meloxicam (Metacam) oral suspension in horses suffering from lameness in comparison to vedaprofen.

A total of 90 horses suffering from lameness due to various musculo-skeletal disorders were included in the study. The mean age was 9.7 years and the mean body weight was 501 kg. The majority of horses were geldings. The most common diagnosis was arthrosis, but a number of different diagnoses occurred, e.g. tendinitis, navicular disease, bone spavin, and laminitis. X-ray examination was performed in 48% of the cases. Horses suffering from fractures were excluded.

The horses were randomly allocated to three treatment groups: Metacam 0.6 mg/kg b.w. once daily for 5 days, Metacam 0.3 mg/kg twice daily for 5 days and vedaprofen dosed according to the approved dosage regimen i.e. 2 mg/kg on the first day followed by 1 mg/kg b.w. daily for four days.

Metacam 0.15% oral suspension for dogs was used. The suspension was mixed with the feed. Vedaprofen was given directly into the mouth according to the manufacturer's instruction.

Lameness at trot was the primary parameter. Lameness was assessed according to a 6-graded scale where 1 means no lameness and 6 means no weight bearing. The study was blinded, the persons assessing lameness were unaware of treatment. The animals were clinically examined prior to treatment and on day 6, one day after the last treatment.

Prior to treatment the lameness score was about 4 in all groups. Treatment reduced lameness in all groups. The scores one day after the last treatment were 2.1 and 2.2 in the Metacam groups and 3.3 in the vedaprofen group. One animal in each group relapsed after cessation of therapy, i.e. the lameness symptoms deteriorated. The score of the group treated once daily with Metacam differed significantly from the score of the vedaprofen group. However, there were no significant changes between the Metacam groups.

Also the overall efficacy assessed after treatment differed in favour of Metacam. A very good rating was achieved for 17% of the horses treated with vedaprofen and for 33% and 37%, respectively, of the horses in the Metacam groups.

The palatability of Metacam appeared to be good.

2) Field study to evaluate the clinical efficacy of meloxicam (Metacam 15 mg/ml oral suspension) in horses with musculoskeletal disorders associated with lameness.

This study was performed at 10 different centres in Germany. A total of 200 horses suffering from lameness in one limb were recruited. The inclusion criteria were the same as in the preceding study. The horses were randomly allocated to two equal groups. One group was treated with the recommended dose of Metacam, the other group with the authorised dose of vedaprofen. The treatment period was 14 days. Metacam was given on the top of the cereal feed and vedaprofen was given directly into the mouth.

Lameness at trot was the primary parameter. Lameness was assessed according to a 7-graded scale where 1 is no lameness and 7 unwillingness to move.

Clinical examination was performed prior to therapy and on days 2 and 5. Based on the results obtained on day 5 the investigator could decide that therapy should be stopped or continue to day 10. Depending on the clinical status therapy could be continued to day 14. A follow up examination was performed 2-4 days after cessation of therapy.

The study was blinded so the investigator was unaware of the therapy.

A total of 197 horses were available for the final evaluation, 97 in the vedaprofen group and 100 in the Metacam group.

The mean lameness score prior to treatment was 4.3 in the Metacam group and 4.1 in the vedaprofen group. The score decreased in both groups during treatment and the scores were lower in the Metacam group at all time points. The difference was statistically significant on day 14 and at the final follow up examination.

The individual improvement of lameness at trot, change versus baseline, revealed significant differences in favour of Metacam on days 5 and 14.

Lameness at walk was considered as a secondary parameter. The scores on day 14 were 1.3 and 1.5, respectively, for Metacam and vedaprofen. Also this small difference was statistically significant.

Relapse of clinical signs was observed for 8% of the horses treated with Metacam and for 21% of the horses treated with vedaprofen. The difference was statistically significant.

The assessment of the overall efficacy (excellent or good clinical response) differed significantly in favour of Metacam at all time points.

All animals of the Metacam group showed normal feed intake during the treatment period, while 2-8% of the animals of the vedaprofen group showed reduced appetite.

No adverse reactions could be observed in the Metacam group. Two horses treated with vedaprofen showed irritated buccal mucosa and increased salivation.

3) Clinical efficacy of a 14-day treatment with meloxicam (Metacam 1.5% oral suspension) in horses with musculoskeletal disorders associated with lameness.

The study was performed at 4 centres in Germany and 10 in France and included 200 horses of which 189 were available for the final evaluation. The inclusion criteria were identical to those in the previous studies.

The efficacy of Metacam was also in this study compared with that of vedaprofen and the drugs were administered as in the previous study. The horses were randomly allocated to the treatment groups. The mean age was about 9 years and the duration of lameness was 10 days in both groups.

The horses were treated for 14 days and clinical examination was performed prior to treatment and on day 7 and day 14. A follow up examination was performed 2-4 days after cessation of treatment.

As in the other studies, lameness at trot was the primary parameter and lameness was assessed according to a 7 graded scale.

The lameness score at trot was 3.9 in both groups prior to treatment and improved during the treatment period. The mean score of the Metacam group was 2.5 and 1.9, respectively, on days 7 and 14, the corresponding scores of the vedaprofen group was 2.7 and 2.9. Both groups showed the score 1.9 at the last follow up examination. The statistical evaluation showed that the efficacy of Metacam was non-inferior to that of vedaprofen.

There were no significant differences for the secondary parameters (lameness at rest, lameness at walk, relapse and feed intake). The palatability of Metacam appeared to be good.

The assessment of the overall efficacy was significantly different at all time points in favour of Metacam. Very good or good efficacy was reported in 84% of the animals of the Metacam group and in 68% of the animals of the vedaprofen group.

Three adverse reactions were observed in the Metacam group, one case of urticaria and two cases of diarrhoea. Five cases occurred in the vedaprofen group, including eczema of the corners of the mouth, swelling of the tongue and the oral mucosa, lymphangitis and loss of appetite.

Further detailed information on the treatment results in acute and chronic cases was provided. The marketing authorisation holder has re-evaluated the results of the clinical trials and the horses were sub-divided into acute (duration of symptoms < 30 days) or chronic cases. (duration of symptoms > 30 days). The majority of cases in the two studies were acute cases (>80%). The primary parameter was lameness at trot. The lameness score was significantly reduced in both groups at days 7 and 14. As expected, the reduction was more pronounced in the acute cases, but the scores differed significantly from the pre-treatment score in both groups. In one of the studies (VU-1557), the investigator could chose between a 5, 10 or 14 day treatment period dependent on the clinical response. In the majority of cases, both acute and chronic, a treatment period of 14 days was chosen.

Risk Benefit Assessment

Metacam 15 mg/ml is intended for treatment of horses suffering from non-infectious musculo-skeletal disorders. The therapeutic index is narrow, but the recommended dose (0.6 mg/kg b.w. for 14 days) appears to be safe. Single intravenous bolus doses of up to 2 mg/kg b.w. was well tolerated in the dose finding study.
The submitted residue depletion study was performed according to current guidelines and the statistical approach recommended by the CVMP (EMEA/CVMP/036/95) was used for estimating the withdrawal period of 3 days. The analytical method used for determination of meloxicam in horse tissues was based on HPLC using UV detection and was fully validated, meeting the requirements of Volume 8 of the Rules Governing Medicinal Products in the European Community regarding minor species.
Previously assessed studies showed that meloxicam is neither a dermal nor an ocular irritant. The person administering the drug is therefore not exposed to any risk and no special precautions are therefore deemed necessary. The appropriate warnings for individuals sensitive to NSAIDs has been included in the SPC as has the advice in case of accidental ingestion. Metacam 15 mg/ml is intended for treatment of individual animals. No herd treatment will occur. The submitted Phase I Assessment of ecotoxicity was, therefore, considered to be sufficient.

The proposed indication for use of Metacam 15 mg/ml is alleviation of pain in both acute and chronic musculo-skeletal disorders. The proposed dose of 0.6 mg/kg b.w. once daily for up to 14 days was estimated using an established experimental carpitis model and PK/PD modelling and was further confirmed in the efficacy studies.

The product can be given either directly into the mouth or mixed with feed. The oral bioavailability of Metacam 15 mg/ml is high (85-96%) and is not reduced when given mixed in feed. The elimination half-life is about 8 hours.
Metacam 15 mg/ml appears to be well tolerated in the target species. Horses treated with the recommended dose for up to 42 days showed no clinical signs and no abnormalities were found at autopsy. After three to five times the recommended dose for 3 times the recommended treatment period, the animals showed typical signs of NSAID toxicity loss of body weight, oedema and ulcerations of the mucosa of the gastrointestinal tract and papillary necrosis of the kidney.
Tolerance was not demonstrated in pregnant mares. However, a relevant warning for use during pregnancy is included in the SPC. In order to add an additional safety span, the marketing authorisation holder proposed to use Metacam only in foals older than 6 weeks and this was considered appropriate.
Efficacy was demonstrated in studies where Metacam 15 mg/ml was compared with a centrally authorised NSAID (vedaprofen) with the same indication. The slightly different formulation was used in a preliminary study where it was shown that the efficacy of 0.3 mg/kg b.w. of meloxicam twice daily was equal to that of 0.6 mg/kg b.w. once daily and to the positive control.
The final formulation of Metacam for horses was used in two multicentre studies. Lameness at trot was the primary parameter in both studies. The horses were treated for up to 14 days. The results showed that the efficacy of Metacam 15 mg/ml given at the recommended dose, 0.6 mg/kg once daily, was equal to or better than that of the centrally authorised comparator drug.
The number of horses included in the studies was sufficiently high to allow valid conclusions. Metacam 15 mg/ml was shown to reduce lameness at trot significantly in both acute and chronic cases. A treatment period of 14 days was required for optimal clinical response in the majority of cases.

VII METACAM CHEWABLE TABLETS FOR DOGS

Quality Assessment

Composition

Metacam chewable tablets are honey flavoured, oval-shaped, pale-yellow, single-scored tablets with embedded code “M 01” (1 mg) and “M 02” (2.5 mg) on one side of the tablet. The tablets contain either 1.0 or 2.5 of mg meloxicam B.P.

Container

White HDPE bottle 1 x 100 chewable tablets together with a desiccant and a child-resistant closure made of polypropylene. PVDC/PE/PVC/Al- child resistant blister with 20, 100 and 500 chewable tablets in cardboard boxes (10 chewable tablets per strip).

Clinical Trial Formula(e)

Equivalence between Metacam 1.5 mg/ml oral suspension and Metacam 1 and 2.5 mg chewable tablets has been demonstrated. The compositions of the formulations were presented in the dossier. Certificates of analysis for the batches used in the clinical trials were also presented.

Development Pharmaceutics

Two strengths of the palatable chewable tablets for veterinary use have been chosen. Extensive experience is available with a similar formulation and stability has been demonstrated in different packaging materials for up to five years. Due to the variability in dog weights it was estimated that 1 mg and 2.5 mg tablets both with score-lines would fulfil the dosing ranges.

The tablets are to be administered by the animal owner for daily chronic treatment and it was thus decided to add a flavour component to improve the palatability. The tablets were developed as an immediate release tablet from a technical point of view and as a chewable tablet due to the palatability requirements. The bulk blend uniformity, the content uniformity of the tablets and the uniformity of tablet halves have been tested. The compatibility with the flavour has been demonstrated with a stress test and has also been shown in the stability tests.

With the exception of honey flavour the excipients are well-known as excipients for tabletting and are all included in Ph. Eur.
Solid honey aroma has been chosen as flavour. The palatability trials in dogs led to the conclusion on the acceptable concentration. This concentration changed neither the immediate release of the tablets nor the robustness of the process.

The final blend is used for both strengths and the drug content per tablet is adjusted by the tablet mass.

50 kg scale batches have been manufactured and tested for content uniformity. The results fulfilled the Ph. Eur. requirements for both the powder blend and the tablets. Three batches were manufactured for stability purposes and tested according to the release specifications. All results were within the specification limits. The manufacturing process is considered validated for the 50 kg batch size at the final manufacturer.

The in-vivo bioequivalence has been demonstrated between Metacam 1.5 mg oral suspension and Metacam 2.5 mg chewable tablets in a study performed on healthy dogs following a single oral administration. Metacam 1 mg and 2.5 mg chewable tablets are considered to be bioequivalent to each other due to that the formulation is the same, the tablet strength is given by the different weights of the tablets.

A discriminating dissolution method has been established. Results from dissolution studies in both HDPE bottles and in PVDC/PE/PVC/Al blisters initially and after storage 3 months at 25ºC/60%RH, 30ºC/70%RH and at 40ºC/75%RH are presented.

The active substance is known to be chemical stable and does not limit the shelf-life of the product. Stability data indicate that the Metacam chewable tablets are rather stable formulations. Photostability studies have been performed to demonstrate that the immediate packaging materials are appropriate. The submitted results from the stability studies are assessed below, see Stability II.F.1 and II.F.2.

Manufacturing at Boehringer Ingelheim Vetmedica Inc., Elwood, USA includes control of the starting materials, manufacture of the finished product including packaging and labelling, analytical controls and finished product shipping. Alternatively packaging, labelling and finished product shipping take place at Boehringer Ingelheim Vetmedica Inc., St. Joseph, USA.

The final EU batch release takes place at Boehringer Ingelheim Vetmedica GmbH, Germany.

Manufacturing formulæ for 50 kg and 500 kg batches were presented as was a manufacturing flow chart.

Control of Starting materials
Active Substance
Specification and routine tests

The quality of the active substance meloxicam conforms with BP. Additional tests on particle size and residual solvents are included. The BP monograph has been prepared in co-operation with Boehringer Ingelheim and is based on the quality obtained by the company. The BP reference standard has been delivered by Boehringer Ingelheim.

The presented specifications for the active substance were considered acceptable.

Meloxicam is practically insoluble in the gastrointestinal fluid and therefore the particle size is controlled. Specifications are provided for the starting materials, auxiliaries and solvents. The specifications for the materials used during manufacture are considered acceptable.

A report on possible impurities was presented. Residual solvent results were also presented. Batch analysis results were submitted and all results were within stated limits.

Excipients

All pharmacopoeial excipients are tested according to the current Ph. Eur. Analysis certificates are submitted. Honey flavour is tested according to the manufacturer's in-house specification. A certificate of analysis was provided.

Packaging Material

The tablets are packed in two different polyethylene bottles and in blister packs:
1) HDPE screw- necked bottle with PP desiccant capsule and a PP child resistant closure, 1 x100 tablets.
2) HDPE screw- necked bottle with PP desiccant capsule and a child resistant closure and a PS - tamper- proof liner, 1 x100 tablets.
3) PVDC/PE/PVC/AL child resistant foil blisters with 20, 100 and 500 tablets in cardboard boxes.

Blister
PVDC/PE/PVC/AL foil. The packaging materials in contact with the product comply with the Commission Directive 2003/72/EC and the current Ph. Eur.

Bottle
An HDPE screw- necked bottle with PP desiccant capsule and a PP child resistant closure. The desiccant is a natural PP-canister with open mesh ends containing silica gel desiccant.
1 mg, 100 tablets in bottle 35 cc, dimensions were provided;
2.5 mg, 100 tablets in bottle 75 cc, dimensions were provided.

The packaging materials in contact with the product comply with Commission Directive 2003/72/EC and current Ph. Eur.

An HDPE screw- necked bottle with PP desiccant capsule and a child resistant closure and a PS tamper-proof liner. The desiccant is a natural PP-canister with open mesh ends containing silica gel desiccant.
1 mg, 100 tablets in bottle 40 cc, dimensions are provided;
2.5 mg, 100 tablets in bottle 75 cc, dimensions are provided.

The packaging materials in contact with the product comply with the current Ph. Eur.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The active ingredient and the excipients used for the production of Metacam chewable tablets are, with the exception of lactose, derived from non-animal origin. Lactose is derived from milk and classified as Category C tissue with no detectable infectivity. The TSE statement for lactose has been completed with information from the suppliers. Lactose is derived from milk sourced from healthy animals in the same conditions as milk collected for human consumption and no other ruminant materials with the exception of calf rennet, are used in the preparation of such derivates.

Control Tests On Finished Product
Product Specification and Routine Tests
The finished products are tested according to the specifications provided. The proposed specification was considered appropriate.
Detailed descriptions for the identification and quantitative determination for the active substance
Scientific Data
Analytical validation of methods and comments on the choice of routine tests and standards were provided

Certificates of analysis have been provided.
Three 50 kg batches have been manufactured. Each batch of the bulk powder has been pressed in both 1 mg and 2.5 mg tablets. Finally each batch of 1 mg and 2.5 mg tablets has been packed in both HDPE bottles and PVDC/PE/PVC/AL blisters. All results were within the stated limits.
Stability
Stability Tests on the Active Substance

Results from storage of three production batches of the substance for up to 60 months at 25°C/60%RH and at 30°C/70%RH and for up to 6 months at 40°C/75%RH were available. No relevant changes were observed.
The proposed retest period is 60 months, stored in the selected packaging material was considered acceptable.

Stability Tests on the Finished Product
Product Specification and Routine Tests for shelf life

Parameters studied and the methods used are in accordance with the testing specifications for the finished product.

The main stability study was performed with three 50 kg batches manufactured at BI Vetmedica Inc. USA. Each batch of the bulk powder has been pressed in both 1 mg and 2.5 mg tablets. Finally each batch of 1.5 mg and 2.5 mg tablets has been packed in both HDPE bottles and PVDC/PE/PVC/AL blisters. The stability studies at 25°C/60%RH, 30°C/70%RH are ongoing and are planned to continue for up to 60 months.

Results from batches that have been stored for 15 months at 25°C/60%RH and at 30°C/70%RH and for 6 months at 40°C/75%RH have been submitted. In addition a photostability study has been performed.

Photostability study

Metacam 1 mg chewable tablets were chosen due to that the lower content is more suspected to degradation. Tablets in bottles, in PVDC/PE/PVC/AL blisters, in Al/Al blisters and active substance in glass vials were tested.

Based on the results it is justified to include "Store in the original package in order to protect from light" for the PVDC/PE/PVC/AL blister package.

As supporting data results from a 5 year stability study with a similar formulation have been submitted. The stability studies are ongoing and the presented stability test results for Metacam 1 mg and 2.5 mg chewable tablets are limited, data covering 15 months at 25°C/60%RH and at 30°C/70%RH and for 6 months at 40°C/75%RH have been submitted. Taken into account the supporting data for the essentially similar product, the proposed shelf-life of 2 years is considered acceptable for Metacam chewable tablet 1 mg (bottles and blisters) and 2.5 mg (bottles).

From the results from storage of Metacam 2.5 mg chewable tablets in blisters at 30°C, limited extrapolation from 15 months to 18 months has been accepted. The shelf life limit may however be reconsidered (not excluding a lowering of the shelf life limit) as real time data (18 months) becomes available. An appropriate commitment has been made.

The storage recommendation "Do not store above 30°C" was based on the test results found during storage at 40°C/75%RH". The recommendation is considered acceptable for Metacam chewable tablet 1 mg (bottles and blisters) and 2.5 mg (bottles). The recommendation for the 2.5 mg tablets in blisters is "Do not store above 25°C". The need for these recommendations should be reconsidered when more data has been achieved. The storage recommendation for the blister, "Store in the original package in order to protect from light", is based on the results from the photo-stability study.

SAFETY ASSESSMENT

No safety studies were performed with the new formulation. This is found to be acceptable as bioequivalence was demonstrated between the Metacam 1 and 2.5 mg chewable tablets and the approved formulation Metacam 1.5 mg/ml oral suspension for dogs.

User Safety

The risk for the operator can be regarded as less for the chewable tablets than for the already approved oral suspensions because spillage on to the skin or into the eyes does not need to be considered.

Ecotoxicity

Metacam chewable tablets are intended for the treatment of individual companion animals. Thus the product has no risk for the environment.

EFFICACY ASSESSMENT

Pharmacokinetics

The pharmacokinetic documentation for Metacam chewable tablets consists of a bioequivalence study where the new formulation is compared to the Metacam 1.5 mg/ml oral suspension for dogs. This study referred to both tolerance and efficacy.

The study had an open, randomised, two-way cross-over design with a 2 week washout period between treatments using 12 healthy dogs. The dogs received an oral dose of 0.2 mg/kg of either Metacam 2.5 mg chewable tablets or Metacam 1.5 mg/ml oral suspension for dogs.. The medication was given in the fasted state. Venous blood samples were collected before and after administration of study medication. The study was conducted in compliance with current GLP guidelines.

Plasma samples were analysed for content of meloxicam. The analytical method used was HPLC with UV detection. A validation report was submitted. The method was found to be valid with respect to accuracy and precision. Conventional non-compartmental pharmacokinetic methods were used.

The test product was compared with the reference product with respect to the pharmacokinetic variables ln C_{max} and ln AUC_{0-t}, using an analysis of variance (ANOVA) and calculation of parametric 90 % confidence limits using the two one-sided t-test procedure for derived pharmacokinetic parameters. Parametric point estimates and 90% confidence intervals for the 'test/reference' mean ratios were calculated. A parameter was considered bioequivalent between the two formulations when the 90% confidence interval of the parameter ratio was within the interval of 0.7 to 1.43 for AUC and C_{max}.

The study was performed according to the current guideline. The wider limits (0.70-1.43) were pre-specified in the protocol and justified with tolerance and pharmacovigilance data showing a large safety margin for the product.

Compared formulations

Trial formulation: Metacam 2.5 mg chewable tablets for dogs
Reference product: Metacam 1.5 mg/ml oral suspension for dogs

The equivalence of the two tablet strengths was tested and confirmed in accordance with the relevant guideline by using in vitro dissolution data.

Mean pharmacokinetic parameters of test and control article:

	Mean ± SD Test article	Mean ± SD Control article
C_{max} (ng/ml)	636 ± 158	554 ± 1.51
AUC_{0-t} (µg/ml.h)	16.6 ± 3.0	13.9 ± 3.0
T_{max} (h)	2.92	2.92

Abbreviations

AUC_{0-t} area under the plasma concentration-time curve from time zero to time-point for last measurable concentration
C_{max} maximum plasma concentration
T_{max} time for maximum concentration

Tolerance in the target species of animal

Objective: 26 week oral toxicity study in the dog on Metacam 1.5 mg/ml oral suspension. Blinded clinical evaluation.
GLP-status: Yes, study performed in accordance with FDA guidelines.
Test formulation: Metacam oral suspension 1.5 mg/ml.
Dose: 0, 0.1, 0.3 and 0.5 mg/kg (stating with a double loading dose at Day 1) administered daily for 6 months.
Animals: 3 dogs of each sex in each group.
Measurements: Clinical observations, body weight and food consumption on scheduled time points before and if relevant 4 h after daily administration. In addition endoscopic and ophthalmic

examinations were performed as well as haematology, clinical pathology and urinalysis. PK data was sampled at 4 occasions (6 samples at each occasion).
Results: No drug related findings were recorded neither at the recommended dose nor at multiple doses (3x, 5x) of the recommended dose. The range in AUC_{24h} at day 1 was 2.64-13.34 µg.h/ml.

Risk Benefit Assessment

The development work on the formulation was considered appropriate and the testing specifications for the active ingredient and excipients were considered acceptable. The manufacturing process is a standard procedure. The critical process parameters have been identified and measures have been undertaken. The process has been validated for 50 kg batch size. A commitment to provide validation of the process for the first three production batches has been submitted. The release and shelf-life specifications or the finished products are considered acceptable and the batch analysis results confirm that the product has an acceptable quality.

The proposed retest period for the active substance is 5 years, in the selected packaging material. Results from storage of three batches of the substance for up to 60 months at 25°C/60%RH, at 30°C/70%RH and for 6 months at 40°C/75%RH are available. No relevant changes were observed. The proposed retest period is considered acceptable.

Results from storage of the finished product have been presented. The batches have been stored for 15 months at 25°C/60%RH and at 30°C/70%RH and for 6 months at 40°C/75%RH.

The storage recommendation "Do not store above 30°C" for Metacam chewable tablet 1 mg (bottles and blisters) and 2.5 mg (bottles) is based on the test results found during storage at 40°C/75%RH". The recommendation for the 2.5 mg tablets in blisters is "Do not store above 25°C".
The proposed shelf-life of 2 years is considered acceptable for Metacam chewable tablet 1 mg (bottles and blisters) and 2.5 mg (bottles). For Metacam 2.5 mg chewable tablets in blisters the shelf life has been set at 18 months.

The need for this recommendation should be reconsidered when more data has been achieved. The storage recommendation for blister "Store in the original package in order to protect from light" is based on the results from the photo-stability study.

The equivalence of the two tablet strengths was tested and confirmed in accordance with the relevant guideline by using in vitro dissolution data.

A new tolerance study after administration of Metacam 1.5 mg/ml oral suspension for dogs was submitted. No drug related findings were recorded.

Bioequivalence with Metacam 1.5 mg/ml oral suspension for dogs was demonstrated.

VIII 2 MG/ML SOLUTION FOR INJECTION FOR CATS

SCIENTIFIC DISCUSSION

An application for an extension of the Community marketing authorisation of Metacam to include a 2 mg/ml solution for injection for cats was submitted to the Agency on 3 March 2009 by Boehringer Ingelheim Vetmedica GmbH in accordance with Article 2(a) of Commission Regulation (EC) No 1085/2003 and Annex II point 2.

Metacam 2 mg/ml solution for injection contains meloxicam and is presented in packs/containers of 10 and 20 ml. It is indicated for "*Alleviation of mild to moderate post-operative pain and inflammation following surgical procedures in cats, e.g. orthopaedic and soft tissue surgery*". This is a new indication that also involves a new dosage regimen that has been assessed for this application. The route of administration is subcutaneous. The target species is cats.

ADMINISTRATIVE PARTICULARS

Pharmacovigilance system
It is considered that the pharmacovigilance system as described by the marketing authorisation holder fulfils the requirements and provides adequate evidence that the marketing authorisation holder has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

GMP
During the assessment of the quality part, there were no signs of non-compliance to GMP that would call for an inspection.

QUALITY

Composition
The finished product Metacam 2 mg/ml solution for injection for cats is a sterile, yellow solution containing meloxicam as active ingredient. The meloxicam solution is intended for multiple use and contains 15% of ethanol as preservative. The formulation also contains meglumine, macrogol 300, poloxamer 188, glycine, disodium EDTA, sodium hydroxide or hydrochloric acid as pH adjusters, and water for injections.

Container
Metacam 2 mg/ml solution for injection is packaged in 10 or 20 ml colourless glass injection vials which are closed with rubber stoppers and crimp-on aluminium caps.

Development Pharmaceutics
The development of the 2 mg/ml meloxicam solution for injection for cats is based on the knowledge and experience of the previously approved meloxicam solution of injection.

The main reason for developing the lower dose 2 mg/ml formulation is that for young and small cats the volume given to the patient of the 5 mg/ml solution will be very small. A more dilute formulation would facilitate a more accurate administration of the product to these smaller animals.

Method of manufacture
The finished product is manufactured according to standard procedures. Adequate process controls are applied. Information on the type of filter used in the manufacturing has been provided.

Satisfactory process validation data have been provided for Labiana Life Sciences S.A., Barcelona, the site of manufacture of drug product.

Control of starting materials

Active substance
The active ingredient, meloxicam, has a monograph in the Ph. Eur (2009:2373) and constitutes a pale yellow powder. The meloxicam substance of this application complies with the requirements of the Ph. Eur. monograph. The marketing authorisation holder has also included additional tests for an residual solvent and particle size in the drug substance specification. The specification for the active substance is considered acceptable. The gas chromatographic method used for determination of the residual solvent has been acceptably validated. A valid qualified person declaration regarding GMP for the drug substance has been provided. Stability data according to VICH guidance for meloxicam have been provided and the data support the proposed re-test period.

Excipients
Details were provided on all excipients used in the formulation. All excipients comply with their respective Ph. Eur. monographs.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A statement from the marketing authorisation holder is provided to the effect that the active substance and the excipients used in the drug product are all derived from non-animal sources. Thus, the ingredients are out of scope of the requirements of the Ph. Eur. 5.2.8 monograph "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" and the "Note for guidance on minimising the risk of Transmitting animal Spongiform Encephalopathy agents via Human and Veterinary Medicinal Products" (EMEA/410/01-Rev.2).

Control tests during production
During manufacture, adequate process controls are applied.

Control tests on the finished product
The proposed release specifications are generally considered justified and supported by the batch analysis data provided. Relevant tests for this dosage form have been included. The specification limit for each individual unspecified impurity is considered justified and in compliance with VICH GL11: Impurities in new veterinary medicinal products (CVMP/VICH/838/99-Rev.1). The identity of the active substance is acceptably verified. The identity and assay of ethanol are determined by gas chromatography and the limits proposed are considered acceptable. Efficacy of antimicrobial preservation has been demonstrated at least at the proposed lower limits for release and shelf life. Batch analysis data have been provided for finished product. All data are within specifications.

Stability
Primary stability studies according to VICH guidelines have been provided for batches of drug product. Also, a 28 days in-use study has been presented and, in addition, a photo-stability study has been performed on the drug product. The primary stability data on the drug product in its marketing package comprise accelerated and long term data up to 12 months. No significant changes in the stability indicating parameters are observed and all results are within specification. The suggested 18 months shelf-life as proposed by the marketing authorisation holder for the finished product is considered acceptable. There is no need for any temperature storage restrictions. An in-use time of 28 days is regarded acceptable based on the in-use stability data provided.

Overall conclusions on quality
The pharmaceutical documentation provided in this application is of sufficient quality according to the regulatory requirement for veterinary products in the EU. The product is manufactured according to standard procedures and is packaged in glass vials closed with rubber stoppers and terminally sterilised. The composition of the product has been justified. The product is tested according to acceptable specifications. The quality of the product is considered adequate.

SAFETY

The marketing authorisation holder refers to data available for Metacam 5 mg/ml solution for injection for dogs and cats (EU/2/97/004/006 and EU/2/97/004/011). It is acceptable not to provide any new data.

The Metacam 5 mg/ml solution for injection for dogs and cats was exempted from a phase II environmental risk assessment. A phase I assessment was provided in the Metacam 5 mg/ml solution for injection for dogs and cats that is sufficient, since the veterinary medicinal product will be used in non-food animals only. User safety has been addressed previously, and the same SPC wording that accidental self-injection may give rise to pain apply here as well.

The local tolerance after parenteral administration was studied in laboratory animals and in dogs. Subcutaneous injection of Metacam solution for injection to rabbits resulted in minor macroscopic and microscopic changes. Reddening of the musculature, small focal haemorrhages in the subcutis and necrosis of single myofibres were the most prominent findings. Similar changes were found in the control group injected with physiological saline.

Similar findings were obtained also after intramuscular injection of Metacam solution for injection. Slight focal skin epithelial necrosis and focal necrosis of muscle fibres were found. Metacam solution for injection was well tolerated in dogs except for slight pain reactions in single individuals. No inflammatory reactions were noted.

For local tolerance in cats, see Efficacy section, target animal tolerance.

EFFICACY

Pharmacokinetics

An ADME study in cats was provided. The aim of the study was to determine the excretion balance and metabolism in cats after oral administration of ^{14}C-meloxicam. The majority of the dose, 79 %, was observed in faeces. The urinary excretion of unchanged meloxicam is low, approximately 2 % of the dose. Approximately 49 % of the dose is observed in the faeces as unchanged meloxicam (may also be unabsorbed to some extent). A slightly revised section 5.2 of the SPC with respect to this section is proposed. For other sections, there is no change to the pharmacokinetic information or the interaction section or other parts of the SPC relating to pharmacokinetics compared to Metacam 5 mg/ml solution for injection for dogs and cats.

Pharmacodynamics

The pharmacodynamic properties of meloxicam have been evaluated in laboratory species, cattle and dogs. Meloxicam is an NSAID of the oxicam class with anti-inflammatory, analgesic and anti-exudative effects.

Target Animal Tolerance

The marketing authorisation holder refers to data provided in previous applications for the 5 mg/ml solution for injection and the 0.5 mg/ml oral suspension. Previous data have for example explored tolerance at dose levels 0.3 and 0.6 mg/kg bodyweight (bw) given as single subcutaneous injections followed by oral treatment at the same dosages for 9 consecutive days. Furthermore in a tolerance study regarding Metacam 5 mg/ml solution for injection no treatment related complications were reported following 3 single daily injections of 0.3 mg/kg bw. The volume administered will be higher for the new formulation, 2 mg/ml solution for injection, at the recommended new dose (0.2 mg/kg bw) as compared to the 5 mg/ml solution, but even a higher volume than for the new solution at recommended dose, was shown to be well tolerated locally according to previous data on the 5 mg/ml solution provided at a dose of 1.5 mg/kg bw during 3 days. Regarding the oral solution, tolerance data are available for up to 90 days exposure which would be sufficient. Regarding tolerance in connection to peri-operative treatment it is noted that total exposure will be higher as compared to the previously

authorised dosing (0.3 mg/kg bw as a single dose) in case oral follow up treatment exceeds 3 days for the new dosing strategy proposed. Tolerance data are available for the 5 mg/ml solution for injection for 3 consecutive injections corresponding to a total exposure of 0.9 mg/kg bw which exceeds the total exposure with the new dosing strategy (cumulative dose 0.4 mg/kg bw if a 4 days-long follow up treatment is applied).

Dose determination / justification

To justify the proposed dosing schedule the marketing authorisation holder refers to data submitted in connection to previous applications. No specific pharmacokinetic data were available for the new dosage schedule but the marketing authorisation holder considers the clinical efficacy for the schedule is proven through the non-inferiority study provided in the current application where Metacam 5 mg/ml solution for injection was administered as a single dose of 0.2 mg/kg bw pre-surgery followed by 0.5 mg/ml oral suspension at a dose of 0.05 mg/kg bw daily for an additional 4 days in connection to orthopaedic surgery in cats. To support the new dosing regimen the marketing authorisation holder further refers to previously submitted population pharmacokinetic modelling which suggests that 0.05 mg/kg bw is sufficient for continuous treatment of chronic disease. However, the marketing authorisation holder acknowledges that this dosing regimen would not be appropriate to initiate control of postoperative pain and thus suggests an initial subcutaneous dose of meloxicam of 0.2 mg/kg bw. Simulated plasma concentration-time profiles of meloxicam at a 0.2 mg/kg loading dose followed by 0.05 mg/kg maintenance dose up to five days is provided to support the suggested dosing regimen. It is agreed that a higher initial dose is justified to ensure an adequate exposure to therapeutic concentrations immediately. However, there are no separate data to support, as single therapy, the new lower dose (0.2 mg/kg bw) for the 2 mg/ml solution for injection. Furthermore, as previously mentioned Metacam 0.5 mg/ml oral suspension (0.05 mg/kg bw) has not previously been evaluated for treatment of post-operative pain. Thus, dose justification was deduced from the outcome of the non-inferiority study and the superiority study study submitted to support the current application.

Field trials

The marketing authorisation holder refers to previously submitted clinical data but the main support for the current application is gained from a new multi-centre blinded and randomised clinical study comparing, in a non-inferiority design, efficacy and safety of meloxicam, applying the suggested new dosing strategy, with tolfenamic acid tablet administration in cats undergoing orthopaedic surgery. The primary endpoint was pain assessment by use of visual assessment score (VAS) scoring. Scoring was performed by visual inspection during 15-30 seconds: pre-surgery, every hour/every second hour until 8 hours after extubation and then twice daily. Secondary endpoints were limb function (4-graded scale) and palatability assessment. The VAS scores were equally high in the two groups before surgery and decreased continuously in a similar pattern in the two groups during the follow-up treatment period. A similar number of animals in each group required rescue analgesia. According to the statistical analysis meloxicam treatment was non-inferior to tolfenamic treatment during the study period. However, this study was not regarded as fully conclusive. In response to this concern the marketing authorisation holder provided information from another study where the post-operative pain alleviating potential of Metacam was compared to placebo treatment including preemptive butorphanol and butorphanol rescue treatment in both treatment groups. In that study cats subjected to surgical procedures involving bone tissue were provided three different loading doses (0.1, 0.2 and 0.3 mg/kg bw) followed by maintenance treatment at a dose of 0.05 mg/kg bw. Pain level after surgery was assessed by several different methods, one of which was identical to the method used as primary endpoint in the non-inferiority study. Additional support for sensitivity of this primary endpoint was gained through comparisons with other methods applied.

Although the new placebo controlled study was not designed to be conclusive from a statistical perspective, it is considered that this study and the information received from the pivotal non-inferiority study provide sufficient support for efficacy with regard to treatment of post-operative pain associated with orthopaedic surgery. However, it was also concluded that Metacam treatment alone may not be sufficient to reduce pain to an acceptable level in case of severe pain and consequently appropriate information to reflect this fact should be inserted in the product information. Palatability was significantly better in the meloxicam group as compared to the tolfenamic group. In the non-

inferiority study, creatinine and also to some extent urea increased during the study in a few cats in both treatment groups. However, considering the more detailed information provided by the marketing authorisation holder in response to this concern it can be concluded that the risk connected to treatment according to the new proposed indication is acceptable in light of the precautions already mentioned in the SPC.

Overall conclusion on efficacy

From data submitted in connection to previous applications administration of Metacam 5 mg/ml solution for injection (0.3 mg/kg bw) as a single dose in connection to soft tissue surgery and ovariohysterectomy, is supported. In the current application a lower dose (0.2 mg/kg bw) is proposed to initiate treatment of peri-operative pain and this single dose may be followed by 0.05 mg/kg bw of Metacam 0.5 mg/ml oral suspension for maximum 4 days. The dose regarding the oral suspension (0.05 mg/kg bw) has previously been accepted for treatment of chronic musculoskeletal disorders but there is no previous information to support efficacy for this dose for treatment of postoperative pain during orthopaedic surgery. Support for the new dosing strategy was thus regarded dependent on the non-inferiority study where cats subjected to fracture surgery were provided the new proposed dosing strategy (2 mg/ml solution for injection, 0.2 mg/kg bw in before surgery followed by 0.5 mg/ml oral suspension, 0.05 mg/kg bw daily for maximum 4 days). According to the results presented this treatment strategy is non-inferior to the positive comparator 6 mg tolfenamic acid tablet provided twice daily (1.5-3 mg/kg bw). However, this study was not regarded as fully conclusive. The marketing authorisation holder responded to these concerns by providing results from a placebo controlled study including preemptive butorphanol and butorphanol rescue treatment in both treatment groups where the pain relieving effect of Metacam was explored after orthopaedic surgery . The results of this study were considered to provide sufficient additional support for effecacy with regard to treatment of post-operative pain following orthopaedic surgery. It was, however, also concluded that Metacam treatment alone may not be sufficient in case of severe pain and a restriction of the indication to reflect this fact was considered necessary.

BENEFIT RISK ASSESSMENT

Introduction

In the current extension application regarding Metacam (meloxicam) 2 mg/ml solution for injection for cats the marketing authorisation holder applies for a new indication: *"alleviation of mild to moderate post-operative pain and inflammation following surgical procedures, e.g. orthopaedic and soft tissue surgery".* The previously approved indication regarding the higher strength of the solution for injection (5 mg/ml) is *"reduction of postoperative pain after ovariohysterectomy and minor soft tissue surgery"* The recommended amount to be administered for this new indication is 0.2 mg/kg bw in connection to surgery. An option to continue treatment for additionally at maximum 4 days with the previously approved 0.5 mg/ml oral suspension (0.05 mg/kg bw) is also suggested. Furthermore it is proposed to maintain, as an alternative for the user, the previously recommended single dose posology by stating that: "single subcutaneous injection of 0.3 mg/kg has also been shown to be safe and efficacious for the reduction of post-operative pain and inflammation. In this case do not use oral follow up treatment".

Benefit assessment

Direct therapeutic benefit

Alleviation of mild to moderate pain in cats *following surgical procedures in cats, e.g. orthopaedic and soft tissue surgery*

Additional benefits

A high treatment compliance and dosing accuracy was noted for meloxicam in the non-inferiority study.

Risk assessment

- Inadequate pain relief

Taking into account that the degree and sensitivity of peri-operative pain may vary between individuals, multimodal pain treatment may be indicated in some cases. This has been addressed by

the inclusion of a specific precaution in the SPC: "*In case additional pain relief is required, multimodal pain therapy should be considered*".

- Adverse reactions

At the recommended dosing regimens, the level of adverse effects after administration of meloxicam is low. Clinical signs are similar to those of other NSAIDs and within acceptable limits and are sufficiently reflected in the SPC. Data submitted in connection to previous applications for meloxicam for use in cats, suggest that the levels of exposure which will occur by use of the new suggested dosing strategy could be tolerated. The marketing authorisation holder has provided sufficient information to conclude that treatment according to the new indication will be associated with acceptable risks provided the precautions already mentioned in the SPC and further advice that "*during anaesthesia, monitoring and fluid therapy should be considered as standard practice*" are taken into account by the prescriber.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the application for the extension to veterinary medicinal product Metacam 2 mg/ml solution for injection for cats is approvable.

Based on the original and complementary data presented, it is concluded that the quality, safety and efficacy of Metacam 2 mg/ml solution for injection for cats in this amended indication were considered to be in accordance with the requirements of Directive 2001/82/EC, as amended.

IX 15 MG/ML ORAL SUSPENSION FOR PIGS

SCIENTIFIC DISCUSSION

An application for an extension of the Community marketing authorisation of Metacam to include a 15 mg/ml oral suspension for pigs has been submitted to the Agency on 1 September 2009 by Boehringer Ingelheim Vetmedica GmbH in accordance with Article 2(a) of Commission Regulation (EC) No 1085/2003 and Annex II, point 2, thereof.

Metacam 15 mg/ml oral suspension for pigs is presented in packs/containers of polyethylene bottles of 100 or 250 ml in a cardboard box. It is indicated in pigs for use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation and for adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy.

The route of administration is oral. The target species is pigs.

ADMINISTRATIVE PARTICULARS

Pharmacovigilance system
The pharmacovigilance system as described by the marketing authorisation holder fulfils the requirements and provides adequate evidence that the marketing authorisation holder has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

During the assessment of the chemical and pharmaceutical documentation no issues have been identified which would trigger an inspection of the manufacturing sites of this marketing authorisation application. The manufacturer is the same as for the approved product Metacam 15 mg/ml oral suspension for horses.

QUALITY

Composition
The finished product Metacam 15 mg/ml oral suspension for pigs contains meloxicam as active ingredient. The formulation also contains hydroxyethylcellulose, sorbitol, xylitol, glycerol, saccharin, honey aroma, and colloidal silica. Sodium benzoate is used as antimicrobial preservative. The chosen concentration preserves the suspension in accordance with the requirements of Ph. Eur. In addition, citric acid, sodium dihydrogen phosphate dihydrate and water are included in the formulation.
Container
Metacam 15 mg/ml oral suspension for pigs is packaged in polyethylene bottles with a tip adapter and a tamper proof child resistant closure. A 10 ml oral syringe with an imprint with lines directly giving the body weight in kilograms corresponding to the actual volume to be given according to the body weight is added to every package.

Development Pharmaceutics
The development of the Metacam 15 mg/ml oral suspension is based on the knowledge and experience of the previously approved oral suspensions.

Method of manufacture
The finished product is manufactured according to standard procedures using conventional techniques and known pharmaceutical excipients. Adequate process controls are applied. Process validation data have been provided.

Control of starting materials

Active substance
The active ingredient, meloxicam, has a monograph in the Ph. Eur (2009:2373) and constitutes a pale yellow powder. The meloxicam substance of this application complies with the requirements of the Ph. Eur. monograph. The marketing authorisation holder has also included additional tests for the residual solvent and particle size in the drug substance specification. The specification is considered acceptable. Stability data according to VICH guidance for meloxicam have been provided and the data support the proposed re-test period.

Excipients
All excipients apart from honey aroma are tested for compliance to the respective monographs in the European Pharmacopoeia. Honey aroma is not described in Ph. Eur. or in any other pharmacopoeia of a Member State but the manufacturer has submitted testing specifications which are considered acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A statement concerning the prevention of the transmission of animal spongiform encephalopathies has been presented. The marketing authorisation holder confirms that the active ingredient and the excipients used for the manufacture of Metacam 15 mg/ml oral suspension for pigs are derived from vegetable source or chemical origin only. The product is therefore out of the scope of Ph. Eur. monograph and of the "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products".

Control tests during production
The in-process specifications are presented. During manufacture adequate process controls are applied.

Control tests on the finished product
The proposed release specifications are considered justified and supported by the batch analysis data provided. The release assay limits for meloxicam of label claim and considered acceptable without further justification. The specification limit for each individual unspecified impurity is considered justified. The identity of the active substance is acceptably verified. Batch analysis data have been provided.

Stability
The main stability study is performed with three batches The batches have been stored for up to 36 months at 25°C/60% RH, at 30°C/70% RH and 12 months at 40°C/70% RH. The results from the tested parameters were all within the specifications.

The viscosity varied over the course of the stability study but at all times up to 24 months the values were within specification.
The meloxicam concentration was within the specifications, the degradation was minimal. The assay of sodium benzoate varied over the course of the study. There was a loss at 40ºC, a slight loss at 30ºC and at 25ºC the content remained almost stable. All results from all time points were within the specified limits.

The samples met the antimicrobial preservative effectiveness test after 36 months storage at 25 ºC. The slight change in sodium benzoate had no effect on the ability to inhibit microbial growth.

The presented stability test result support the proposed shelf-life of 3 years.
The proposed in-use stability of 6 months is considered acceptable.

Overall conclusions on quality
The current application for the 15 mg/ml meloxicam oral suspension for pigs is a line extension to the previously approved 15 mg/ml meloxicam oral suspension for horses.
The pharmaceutical documentation provided in this application is of sufficient quality according to the regulatory requirement for veterinary products in the EU. The drug substance meloxicam complies with the Ph. Eur. monograph. The product is manufactured according to standard procedures and is packaged in polyethylene bottles with a tip adapter and a tamper proof child resistant closure. The composition of the product has been justified. The product is tested according to generally acceptable specifications.

SAFETY

Pharmacodynamics
No specific pharmacodynamic study with this formulation has been performed and none is needed.

Pharmacokinetics
The pharmacokinetic studies provided in support of addition of a new target species for Metacam oral suspension 15 mg/ml are described in Part 4.
Toxicological studies

No new studies have been performed and none are needed.

Studies of other effects

No studies have been performed and none are needed.

User safety

Previously assessed studies showed that meloxicam is neither a dermal nor an ocular irritant. The person administering the product is therefore not exposed to any risk. Otherwise, user safety is considered acceptable when used according to the product information.

Environmental risk assessment
A previously assessed calculation of Predicted Environmental Concentrations in soil showed that the trigger value of the current VICH phase I guideline (EMEA/CVMP/VICH/592/98-FINAL) was not exceeded.

Overall conclusions on the safety documentation
Metacam 15 mg/ml oral suspension appears to be safe when used as recommended. It will not result in any harmful effects on the environment and does not pose any risk for the person administering the product. Warnings on the product information that "*People with known hypersensitivity to Non-Steroidal Anti-inflammatory Drugs (NSAID) should avoid contact with the veterinary medicinal product*" and "*In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician*" are considered sufficient.

Residues documentation

Residue studies

Pharmacokinetics
The pharmacokinetic studies provided in support of addition of a new target species for Metacam oral suspension 15 mg/ml are described in Part 4.

Depletion of residues
No new studies are provided and none are needed.

MRLs
Currently, meloxicam is included in Table 1 of the Annex of Regulation (EU) No 37/2010 listing allowed substances, with the details for porcine species in accordance with the following table:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Meloxicam	Meloxicam	Porcine	20 µg/kg 65 µg/kg 65 µg/kg	Muscle Liver Kidney	No entry	Anti-inflammatory agents/ Non-steroidal anti-inflammatory agents

The excipients included in Metacam 15 mg/ml oral suspension (according to the qualitative and quantitative composition) are either included in Table 1 of the Annex of Regulation (EU) No 37/2010 or considered as not falling within the scope of Regulation (EC) No 470/2009 and do not present any risk for the consumer.

Withdrawal periods
A withdrawal period of 5 days is proposed for pigs after administration of Metacam 15 mg/ml oral suspension at the recommended dosage. This is based on the previously assessed residue depletion studies performed with Metacam 20 mg/ml solution for injection. This study was also used when establishing a withdrawal period for Metacam 5 mg/ml solution for injection. Pharmacokinetic data provided showed that bioequivalence was obtained with respect to extent between the 5 mg/ml intramuscular injection and the 15 mg/ml oral suspension. In the residue studies performed with Metacam 20 mg/ml solution for injection the injection site residues were the critical point for the withdrawal period and that is no matter of concern following oral treatment. Consequently, the results from the residue depletion studies performed with Metacam 20 mg/ml solution for injection can be considered as a worst-case scenario concerning the safety of the consumer.

Analytical methods
No new studies are provided and none are needed.

Overall conclusions on the residues documentation
A withdrawal period of 5 days for meat and offal from pigs treated with Metacam 15 mg/ml oral solution is considered acceptable.

EFFICACY
One pilot and one pivotal pharmacokinetic study were performed in support of addition of a new target species for Metacam oral suspension 15 mg/ml. The pilot study in pigs evaluated if bioequivalence could be established between 15 mg/ml oral suspension and 20 mg/ml solution for intramuscular injection at a dose of 0.4 mg/kg for both treatments. One finding (although a small study) was the large deviations in the ratio of Cmax in fasting conditions compared to intramuscular injection, and compared with the ratio in fed conditions for Cmax (within the same study). The conclusions drawn from the pilot study should be made with caution, however in fasting conditions there seem to be a delay in the absorption. Therefore it is specified that the product should preferably be administered with food.

In the pivotal study in fed conditions in pigs, where 5 mg/ml solution for intramuscular injection was compared to 15 mg/ml oral suspension, studied with the same dose as in the first study, 0.4 mg/kg, bioequivalence was obtained with respect to extent but not to rate of absorption. Based on the conditions applied for, non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation and for adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (Mastitis-Metritits-Agalactia syndrome) with appropriate antibiotic therapy, there should be no request for an additional efficacy study. The following wording is used in the SPC with respect to the MMA-indication: "*In cases of MMA with severely disturbed general demeanour (e.g. anorexia) the use of Metacam 20 mg/ml solution for injection is recommended.*"

Pharmacodynamics
Meloxicam is an NSAID of the oxicam class with anti-inflammatory and analgesic effects. No specific pharmacodynamic study with this formulation has been performed and none is needed.

Target Animal Tolerance
Metacam 15 mg/ml oral suspension was well tolerated in the bioequivalence study performed in pigs. Reference is otherwise made to previously performed target animal tolerance studies performed with the 20 mg/ml solution for injection at a dose 5 times higher than the labelled dose of 0.4 mg/kg.

Dose determination / justification
Pharmacokinetic data have established bioequivalence in terms of extent but not rate of absorption between the 5 mg/ml intramuscular injection and the 15 mg/ml oral suspension administered the same dose of 0.4 mg/kg. The indication MMA syndrome is not included in the SPC of Metacam 5 mg/ml solution for injection, but approved for the 20 mg/ml solution for injection. The reason is that the higher strength is more appropriate for higher weight animals. CVMP agreed upon therapeutic equivalence between the two strengths. Although the pivotal bioequivalence study was performed with the 5 mg/ml solution for injection, it is possible to extrapolate the approved indication for Metacam 20 mg/ml "*For adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (mastitis-metritis agalactia syndrome) with appropriate antibiotic therapy"* to the current formulation Metacam 15 mg/ml oral suspension.

Dose confirmation
The bioequivalence studies submitted are considered sufficient. Appropriate additional SPC wordings in relation to the MMA indication have been included.

Field trials
No other studies have been performed and none are needed.

Other studies
No other studies have been performed and none are needed.

Overall conclusion on efficacy
Given the bioequivalence shown with respect to extent of absorption between the Metacam 5 mg/ml solution for injection and Metacam 15 mg/ml oral suspension, similar efficacy and systemic safety can be assumed in locomotor disorders. Regarding the MMA indication, additional SPC-wordings, stating that the solution for injection may be more appropriate to use in certain cases, are included. SPC wordings have been also included stating that the product should preferably be administered with food.

BENEFIT RISK ASSESSMENT
Introduction

- Metacam 15 mg/ml oral suspension for pigs, active ingredient meloxicam
- Extension application to include a new animal species for an approved suspension formulation to horses. It also means a new route of administration to pigs.

Benefit assessment

Direct therapeutic benefit
Meloxicam is a well known active substance, being effective in pain relief due to its inhibitory effect on prostaglandin synthesis. The bioequivalence study can be used to extrapolate the clinical efficacy and safety data obtained with the intramuscular injection 5 and 20 mg/ml. The data were accepted as a basis to use the product in the following condition:

For use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation.

Regarding the MMA indication, additional SPC-wordings, stating that the injection solution may be more appropriate to use in certain cases, are included:

For adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy.

Additional benefit
A benefit in comparison to intramuscular administration as a result of decreased stress to the pig is likely. The product will be easier to apply to food than the current injection procedure.

Risk assessment
The product information states in sections 4.3 and 4.5 (in accordance with the approved intramuscular 5 and 20 mg/ml solution formulations):

4.3 Contraindications
Do not use in animals suffering from impaired hepatic, cardiac or renal function and haemorrhagic disorders, or where there is evidence of ulcerogenic gastrointestinal lesions.
Do not use in case of hypersensitivity to the active substance or to any of the excipients.

4.5 Special precautions for use
Special precautions for use in animals
If adverse reactions occur, treatment should be discontinued and the advice of a veterinarian should be sought. Avoid use in very severely dehydrated, hypovolaemic or hypotensive animals which require parenteral rehydration, as there may be a potential risk of renal toxicity.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
People with known hypersensitivity to Non-Steroidal Anti-Inflammatory Drugs (NSAID) should avoid contact with the veterinary medicinal product.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Risk management or mitigation measures
As per the product information.

Evaluation of the benefit risk balance
The product has been shown to have a positive benefit risk balance overall. Based on the bioequivalence studies, extrapolation to use this product in the indication non-infectious locomotor disorders to reduce the symptoms of lameness can be accepted. Appropriate SPC wordings in relation to pigs suffering from MMA have been included. It is now stated that the 20 mg/ml injection solution may be more appropriate in certain cases.

The formulation and manufacture of Metacam 15 mg/ml oral suspension for pigs are well described and specifications set will ensure that product of consistent quality will be produced.

The product is well tolerated by the target animals and presents a low risk for users and the environment and appropriate warnings has been included in the SPC. A withdrawal period in accordance with the intramuscular injection formulation has been set, 5 days for meat and offal.

Conclusion on benefit risk balance
The overall benefit risk evaluation is deemed positive.

Conclusion
Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that for the application for the Metacam 15 mg/ml oral suspension for pigs, the overall benefit risk evaluation is deemed positive with a sufficiently clear and complete SPC and product literature.

Based on the original and complementary data presented, it is concluded that the quality, safety and efficacy of Metacam 15 mg/ml oral suspension for pigs were considered to be in accordance with the requirements of Directive 2001/82/EC, as amended.