SCIENTIFIC DISCUSSION

Invented name:	Novem
International Non-proprietary Name:	Meloxicam
Target species:	Cattle & Pigs
Therapeutic indication:	**Novem 5 mg/ml** **Cattle:** For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle. 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. **Pigs:** For use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation. **Novem 20 mg/ml** **Cattle:** For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle. 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. For adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy. **Pigs:** For use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation. For adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy.
Withdrawal period:	Cattle: Meat and offal: 15 days; Milk: 5 days Pigs: Meat and offal: 5 days.
Pharmaceutical form:	Solution for injection
ATCvet code	ATCvet code: QM01AC06
Pharmaco-Therapeutic Group	Non Steroidal Anti-inflammatory
Marketing Authorisation Holder :	Boehringer Ingelheim Vetmedica
Product type:	Pharmaceutical

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NOVEM 5MG/ML

Novem 5 mg/ml solution contains meloxicam, a non steroidal anti-inflammatory product developed for veterinary use.

The application for Novem 5 mg/ml solution for injection was submitted according to Article 13.1.a (i) of Directive 2001/82/EC of the European Parliament and of the Council. The Applicant was, therefore, not required to provide the results of toxicological, pharmacotoxicological tests and clinical trials as Novem 5 mg/ml solution for injection is essentially similar to Metacam 5 mg/ml solution for injection which was authorised by the European Commission via the Centralised Procedure on 7 January 1998. The Commission approved the renewal of the authorisation on 17 March 2003 (with effect from 7 January 2003).

The Marketing Authorisation Holder, Boehringer Ingelheim Vetmedica, self-consented to the data contained in the original files for Metacam 5 mg/ml solution for injection being used for the purpose of examination of Novem 5 mg/ml solution for injection; reference to the assessment of Metacam 5 mg/ml solution for injection is therefore made below.

QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

COMPOSITION OF THE VETERINARY MEDICINAL PRODUCT

The product contains the following active ingredient and excipient, the knowledge of which is essential for the proper administration of the veterinary medicinal product;

Ingredient	Amount [mg/ml]	Function
Meloxicam B.P.	5.00	Active ingredient
Ethanol anhydrous* (Ph.Eur.)	150.00	Preservative

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

CONTAINER

The containers are colourless glass, Type 1, with rubber stoppers.

CLINICAL TRIAL FORMULATION

Data for both the 5 mg/ml solution for injection and a single dose formulation without ethanol were presented. The solvent is unlikely to affect bioavailability of the product.

DEVELOPMENT PHARMACEUTICS

The active ingredient meloxicam is an achiral drug substance with poor aqueous solubility. The solubility is increased by alkalising agents; 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 stopper that was chosen offered optimal physical properties and compliance with the requirements of Ph. Eur.

METHOD OF PREPARATION

The product is manufactured and heat sterilised with a standard procedure without apparent decomposition (LOQ 0.5 %).

CONTROL OF STARTING MATERIALS

The active ingredient meloxicam is a known active substance in medicines for human use and those in animals. It is described in the British Pharmacopoeia.

The quality control of the active ingredient was considered adequate. The purity profile and purity level did not differ significantly in drug substance from the alternative manufacturers. The impurity profiles of three batches produced during 1994 at Dr. K. Thomae GmbH and Bidachem S.p.A. were compared. The total level of related impurities was low, $\leq$ 0.03 % for all batches. All the individual impurities were $\leq$ 0.01 %. Unknown impurities were not referred to by any attribute and the number of peaks observed was not stated. There was no significant difference in quality dependent on production site judged from the numerical data. The impurity level was the same as shown for representative batches used in clinical trials but no data of batches used in toxicological studies were reported in Part II.

Residual solvent results were reported.

CONTROL TESTS CARRIED OUT 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 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 pre-formulation 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 %).

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. A subsequent variation was approved (see below) to increase the shelf-life of the finished product to 36 months.

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 shelf- life of 28 days was approved for the preserved multi-dose container.

Light exposure was also investigated. The results indicate that light exposure does not affect the quality of the product.

SPECIFIC MEASURES CONCERNING THE PREVENTION OF THE TRANSMISSION OF ANIMAL SPONGIFORM ENCEPHALOPATHIES

The product contains no material of bovine origin.

OVERVIEW OF PART III OF THE DOSSIER: TOXICOLOGICAL AND PHARMACOLOGICAL ASPECTS

Safety:

Toxicological studies

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 bw, in the 52-week feeding study in Wistar rats as well as after intravenous treatment for 4 weeks in Chbb:THOM rats. Minipigs were relatively insensitive to meloxicam with a NOEL of 1 mg/kg bw derived from a 13 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 bw) 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 bw) can be regarded as a LOEL. The NOEL for embryotoxic effects in Sprague Dawley rats was 1 mg/kg bw.

Teratogenicity studies have been performed in rats (strains: Sprague Dawley and Chbb:THOM) and Chbb:HM rabbits at doses of 1-4 mg/kg bw 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 bw 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 bw 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.

An ADI of 1.25 μg/kg bw (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.

User 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 SPC. Furthermore, as there may be individuals sensitive to NSAIDS, it was also considered necessary to have a suitable statement in the SPC.

Ecotoxicity

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.

RESIDUE DOCUMENTATION

Metabolism and residue kinetics

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.

Residue depletion studies

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

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.

MRLs for meloxicam have been established 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	

Withdrawal period

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.

OVERVIEW OF PART IV OF THE DOSSIER: CLINICAL ASPECTS

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.

Pharmacokinetics:

see Section III.

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.

CLINICAL STUDIES

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.

An open, controlled and randomised multi-centre study was also performed previously with calves suffering from diarrhoea and dehydration. The combination treatment with Metacam 5 mg/ml and rehydration solution was shown to be superior to rehydration solution alone.

EXTENSION TO PIGS:

The application for Novem 5 mg/ml solution for injection for cattle (EU/2/04/042/001 and EU/2/04/042/002) was submitted according to Article 13.1 a (i) of Directive 2001/82EC of the European Parliament and of the Council. Reference is made to the already centrally registered Metacam 5 mg/ml solution for injection for cattle and pigs (EU/2/97/004/001 and EU/2/97/004/010). It is noted that Novem 5 mg/ml solution for injection for cattle and pigs should be identical to Metacam 5 mg/ml solution for injection for cattle and pigs except for the different trade name and the absence of the intravenous administration route in cattle.

SAFETY ASSESSMENT (PHARMACO-TOXICOLOGICAL)

CLINICAL ASSESSMENT (EFFICACY)

Basic pharmacokinetic parameters for meloxicam in pigs were earlier presented. Half-life 2.5 hours, Cl 1.56 ml/min/kg b.w., V_d 0.31 l/kg b.w. Moreover, bioequivalence was demonstrated for Metacam 5 mg/ml and Metacam 20 mg/ml.

Field trials

The results of a double-blind placebo-controlled multicenter study including 211 pigs in the per-protocol population suffering from non-infectious locomotor disorders were earlier submitted. The body weight of the pigs ranged from 20 to 300 kg. One hundred and seven pigs were treated with meloxicam at the dose 0.4 mg/kg body weight. The treatment could be repeated once after 24 hours if necessary. The Clinical Lameness Score improved significantly in the treated group when compared with the controls. No adverse reactions occurred.

RISK-BENEFIT ASSESSMENT AND CONCLUSION

The application for Novem 5 mg/ml solution for injection was submitted according to Article 13.1.a (i) of Directive 2001/82/EC of the European Parliament and of the Council. The Applicant was, therefore, not required to provide the results of toxicological, pharmaco-toxicological tests and clinical trials as Novem 5 mg/ml solution for injection is essentially similar to Metacam 5 mg/ml solution for injection which was authorised by the European Commission via the Centralised Procedure on 7 January 1998.

The Marketing Authorisation Holder, Boehringer Ingelheim Vetmedica self-consented to the data contained in the original files and subsequent files for Metacam 5 mg/ml solution for injection being used for the purpose of examination of Novem 5 mg/ml solution for injection.

As the dossiers were identical, the Committee for Veterinary Medicinal Products concluded that the quality, safety and efficacy of the product had been previously demonstrated and were therefore considered to be in accordance with the requirements of Directive 2001/82/EC of the European Parliament and of the Council.

An extension of the Community Marketing Authorisation for Novem 5 mg/ml solution for injection for cattle to pigs was submitted in accordance Annex II of Commission Regulation (EC) No. 1085/2003. The application was for an additional indication for use in the already registered target species cattle (i.e. diarrhoea in combination with oral re-hydration therapy) and for an additional target species (pigs) to the centrally registered Novem 5 mg/ml solution for injection for cattle (EU/2/04/042/001 and EU/2/04/042/002). Reference is made to the already centrally registered Metacam 5 mg/ml solution for injection for cattle and pigs (EU/2/97/004/001 and EU/2/97/004/010). It should be noted that Novem 5 mg/ml solution for injection for cattle and pigs is identical to Metacam 5 mg/ml solution for injection for cattle and pigs except for the different trade name and the absence of the intravenous administration route in cattle.

As the dossiers are identical it can be concluded that the quality, safety and efficacy of the product have previously been demonstrated.

NOVEM 20 MG/ML

Novem 20 mg/ml solution contains meloxicam, a non steroidal anti-inflammatory product developed for veterinary use. The product has the following indications;

Cattle:

For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle. 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. For adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy.

Pigs:

For use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation. For adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy.

The product is presented in colourless glass injection vials of 50 ml and 100 ml.

The application for Novem 20 mg/ml solution for injection was submitted according to Article 13.1.a (i) of Directive 2001/82/EC of the European Parliament and of the Council. The Applicant was, therefore, not required to provide the results of toxicological, pharmacotoxicological tests and clinical trials as Novem 20 mg/ml solution for injection is essentially similar to Metacam 20 mg/ml solution for injection which was authorised by the European Commission via the Centralised Procedure on 23 April 2001.

The Marketing Authorisation Holder, Boehringer Ingelheim Vetmedica, self-consented to the data contained in the original files for Metacam 20 mg/ml solution for injection being used for the purpose of examination of Novem 20 mg/ml solution for injection; reference to the assessment of Metacam 20 mg/ml solution for injection is therefore made below.

QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

Composition of the veterinary medicinal product

The product contains the following active ingredient and excipient, the knowledge of which is essential for the proper administration of the veterinary medicinal product;

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

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

Container

Colourless glass injection vials of 50 ml and 100 ml sealed with a rubber stopper.. Both packaging materials conform to the European Pharmacopoeia Monograph (Ph. Eur). The closures have been tested for fragmentation and self-sealing.

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.

DESCRIPTION OF METHOD OF PREPARATION

Manufacturing formula

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.

Manufacturing process

The manufacturing process was also described and shown in a flowchart.. 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. In-process controls include check of appearance, pH, relative density, filter integrity test, filling mass, and completeness of solution (clear solution, free of particles).

Validation of the manufacturing process

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. Meloxicam is included in the British Pharmacopoeia.

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

All the inactive ingredients comply with the European pharmacopoeia. It was confirmed that the water for injections (in bulk) complies with the monograph of the current Ph. Eur. and a certificate of analysis was submitted.

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 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 one of the excipients 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 Applicant has also provided additional data.

Three batches have been stored up to 36 months at 25°C/60 %RH and at 30°C/70 %RH. The batches were also stored at 40°C ambient humidity and two of them were re-stored at 40°C 75% for up to 6 months. One additional batch was stored at 40°C 75% for up to 6 months. No degradation could be observed and no relevant changes were observed for the following test parameters: appearance, odour, clarity of solution, melting point, and assay.

The stability study with the active ingredient was ongoing and would be completed after a period of 60 months. A report with data from 60 months of storage was under preparation and would be submitted as soon as available. The Applicant concludes that based on the available stability data the re-test period is set to 60 months. After this period the batch will be re-tested for compliance with the specifications and then used immediately, which is understood to be within 30 days.

The proposed re-test period of 60 months is considered acceptable.

Stability tests on the finished product

Stability studies have been started with three production scale batches. The Applicant 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.

During the longterm stability testing no samples were stored in an inverted position due to the fact that the concentration of preservative is independent of the orientation of the vials. This is supported by stability tests carried out with a pilot-scale batch (20 L) as described in the development pharmaceutics. These samples have now been stored in an inverted and upright position for 36 months at 25°C/60% RH. No significant decrease of ethanol has been observed. The finding is supported by the stability studies carried out with Metacam 5 mg/ml solution for injection in which the vials were stored horizontally. The data shows that the concentration of ethanol in Metacam 20 mg/ml solution for injection is independent of the orientation of the vials during storage. A variation to increase the shelf life of the finished product to 3 years was accepted by the EMEA in July 2003.

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.

Light exposure was also investigated. 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.

II Q OTHER INFORMATION

A statement with regard to the risk from BSE has been provided; no material of bovine origin is used in the manufacture of the product.

OVERVIEW OF PART III OF THE DOSSIER: TOXICOLOGICAL AND PHARMACOLOGICAL ASPECTS

SAFETY

Pharmacodynamics

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class which acts by inhibition of prostaglandin synthesis, thereby exerting anti-inflammatory, anti-exudative, analgesic and antipyretic properties. Meloxicam also has anti-endotoxic properties because it has been shown to inhibit production of thromboxane B_2 induced by intravenous *E. coli* endotoxin administration in calves.

An experimental study was designed to demonstrate the antipyretic effect of meloxicam in cattle by determination of changes of responses to intravenous *E.coli* endotoxin. The concentration of thromboxane B2 was significantly increased at 2, 4, and 6 hours after endotoxin treatment. Meloxicam abolished the thromboxane B2 response almost completely. The mean plasma meloxicam concentration was 3220.8 ng/ml after 2 hours and had decreased to 2180.5 ng/ml at 24 hours. The antipyretic effect of meloxicam was demonstrated in the study.

(This study was also included in the original dossier for Metacam solution for injection 5 mg/ml for cattle).

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.

III A. 3 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 bw (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 og 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 Applicant is acceptable.

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

III. A.4 Studies of other effects

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

III. A.5 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.

III.A.6 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.

III.B RESIDUE DOCUMENTATION

III.B.1 Precise Identification of the Substance

See Part II.

III.B.2 Detection of Residues

Cattle

Sixteen cattle were given a single subcutaneous injection of 0.5 mg ^{14}C-meloxicam/kg bw (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 bw (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

^{14}C-Meloxicam: Metabolism and residues in tissues following intramuscular administration to pigs (VU – 01486).

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 bw 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 sacrified 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 sacrified 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	Inj.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 methabolic 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

Tissue	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.

III.B.2.3. Maximum Residue Limits (MRLs)

Currently, meloxicam is 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	

The excipients used are 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).

Meloxicam is included in Annex I with the MRLs 25 µg/kg, 60 µg/kg and 35 µg/kg for muscle, liver and kidney, respectively, and 15 µg/kg for milk. 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.

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

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.

III.B.2.4 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 the 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 bw (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 Applicant.

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 slaughted 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.

III.B.3 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.

OVERVIEW OF PART IV OF THE DOSSIER: CLINICAL ASPECTS

PRE-CLINICAL STUDIES

IV.I.A.1 Pharmacodynamics

See Part III.

IV.I.A.2 Pharmacokinetics

Pigs

One study documenting the pharmacokinetics of meloxicam in swine 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 (VU- 01486)
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 sacrified 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 sacrified 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.

See also Section III B 2.2.

IV.I.B 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.

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 bw, 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.

IV.II CLINICAL STUDIES

A number of efficacy studies in calves included in the original dossier for Metacam solution for injection 5 mg/ml and previously assessed were re-submitted. It is not considered relevant to re-examine these studies on which the approved claim is based. Only the studies pertaining to the new claims are assessed below.

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

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 Califronia 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 bw, the cows in the other group were treated intravenously with flunixin, 2.2 mg/kg bw 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.

The results of the study demonstrated that meloxicam and flunixin reduced the clinical signs of mastitis to the same extent. The indication "For adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy," is considered to be supported.

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 in study VU-01524 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 demeneaour, 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 demeneaour, 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 relaps 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 euthanised during the study. One further sow of the Metacam group was euthanised 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 septicemia 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.

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

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 eleven swine with non-infectious locomotor disorders were included in the per-protocol population of 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 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 efficious 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.

RISK-BENEFIT ASSESSMENT AND CONCLUSION

The application for Novem 20 mg/ml solution for injection was submitted according to Article 13.1.a (i) of Directive 2001/82/EC of the European Parliament and of the Council. The Applicant was, therefore, not required to provide the results of toxicological, pharmacotoxicological tests and clinical trials as Novem 20 mg/ml solution for injection is essentially similar to Metacam 20 mg/ml solution for injection which was authorised by the European Commission via the Centralised Procedure on 23 April 2001.

The Marketing Authorisation Holder, Boehringer Ingelheim Vetmedica self-consented to the data contained in the original files for Metacam 20 mg/ml solution for injection being used for the purpose of examination of Novem 20 mg/ml solution for injection.

As the dossiers were identical, the Committee for Veterinary Medicinal Products concluded that the quality, safety and efficacy of the product had been previously demonstrated and were therefore considered to be in accordance with the requirements of Directive 2001/82/EC of the European Parliament and of the Council.

