SCIENTIFIC DISCUSSION

1. SUMMARY OF THE DOSSIER

The submission of the marketing authorisation application for Melovem was in accordance with Article 13(1) of Directive 2001/82/EC, as amended, which refers to applications for veterinary medicinal products which are generics of a reference medicinal product authorised within the Community. In accordance with this provision, 'Melovem 5mg/ml Solution for Injection' is a generic of 'Metacam 5 mg/ml Solution for Injection' (Marketing Authorisation Holder: Boehringer Ingelheim Vetmedica GmbH).

The product 'Novem 5mg/ml Solution for Injection' was also referred to in the dossier. This product was the subject of an application for authorisation through the centralised procedure in accordance with Article 13.1.a(i) of Directive 2001/82/EC ('informed consent') and 'Metacam 5 mg/ml Solution for Injection' was the reference product. Given that 'Novem' was authorised on the basis of informed consent, 'Novem 5mg/ml Solution for Injection' and 'Metacam 5mg/ml Solution for Injection' can be considered the same.

Melovem contains meloxicam at a concentration of 5 mg/ml and is to be used in cattle in cases of acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs, and in calves of over one week of age and young, non-lactating cattle in cases of diarrhoea in combination with oral re-hydration therapy to reduce clinical signs. In pigs Melovem is used in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation.

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 E. coli endotoxin administration in calves and pigs.

The recommended posology is as follows:

Cattle:
Single subcutaneous injection at a dosage of 0.5 mg meloxicam/kg body weight (i.e. 10.0 ml/100 kg bodyweight) in combination with antibiotic therapy or with oral re-hydration therapy, as appropriate.

Pigs:
Single intramuscular injection at a dosage of 0.4 mg meloxicam/kg body weight (i.e. 2.0 ml/25 kg bodyweight). If required, a second administration of meloxicam can be given after 24 hours.
It is recommended to administer the second injection at a different site since local tolerance has been assessed after single injection only.

2. QUALITY ASSESSMENT

Composition of the Veterinary Medicinal Product

As active substance Melovem contains meloxicam 5 mg/ml and as excipient benzyl alcohol at 50 mg/ml. Other excipients include hydrochloric acid, sodium chloride, macrogol 400, macrogol 1500, meglumine and water for injection. There are no overages used in the formulation.

Container

The container is a 100 ml type I colourless glass vial with a grey type I rubber bromobutyl stopper and aluminium cap.

Clinical Trial Formula

Details of the clinical trial formula were provided and these were identical to the final composition submitted in the dossier.

Development Pharmaceutics

The product formulation was developed with reference to that of the reference product Metacam. Detailed information was provided regarding the physical and chemical properties of all the components. Formulation development was conducted in order to optimise the formulation, particularly the solubilising agents and antimicrobial preservative used in the product. Several trial batches were manufactured and the final formulation selected on the basis of physical and chemical stability studies. The selected solubilising agents (Macrogol 400 and Macrogol 1500) are widely used in pharmaceutical products and whilst ethanol is the preservative in the reference product the applicant preferred to use an alternative antimicrobial preservative benzyl alcohol. Developmental studies conducted on the formulation confirmed its stability. A slight reduction in pH following autoclaving of the formulation is compensated for by an adjustment in the target pH during manufacture prior to sterilisation. This ensures that the target pH for the formulation is achieved.

The manufacturing process is a standard one. The product is subjected to a sterile filtration step prior to terminal sterilisation in order to minimise the bioburden levels prior to terminal sterilisation. Furthermore the vials and rubber stoppers are sterilised prior to terminal sterilisation.

The product is packaged in type I glass vials and the stopper is a type I bromobutyl rubber closure suitable for aqueous preparations. The physical and chemical proprieties of the packaging materials were described with respect to their suitability for use with the product. Self-sealing tests in accordance with Ph. Eur. requirements have been conducted.

Compatibility of the container /closure system and the product was confirmed by the stability studies which have been conducted with vials stored in an inverted position. Results were presented in the dossier. The packaging materials are widely used for injectable formulations and are of the highest quality specified in the Ph. Eur. They are considered suitable for use with the product.

The data provided in the dossier is sufficient to provide assurance that the generic product is comparable to the reference product with respect to impurity profile as well as physico-chemical characteristics. Justification of the release specification was provided.

METHOD OF MANUFACTURE

Manufacturing Formula and Batch Size

The manufacturing formula was provided for the proposed batch sizes. No adjustment is made for active substance potency as the specification is sufficiently tight to ensure the accuracy of the formulated batch. No overages are included in the formulation.

Manufacturing Process and In-process Controls

The manufacturing process is a standard one involving sequential addition of the components to a portion of water with mixing conducted after each addition. The product is filled under an inert gas in order to prevent the ingredients from potential oxidation during storage of the product. A satisfactory flow chart of the procedure was provided.

The primary method of sterilisation is terminal sterilisation in the final container according to the Ph. Eur. standard cycle. In order to ensure a low bioburden prior to autoclaving, the solution is sterile filtered. Vials and closures are also sterilised prior to autoclaving.

In-process controls are specified in the description of the manufacturing process, on the flow chart and as a separate table in the dossier. They consist of:

- Bulk solution: appearance, pH, relative density
- Sterile filtration: filter integrity, bioburden prior to filtration
- Filling: fill volume at 15 minute intervals
- Terminal sterilisation: Process parameter control / monitoring.

Validation of Manufacturing Process

Process validation has been conducted on a number of pilot scale batches. As the process is a standard one, the validation consisted of conducting in-process controls and testing of the finished product in line with its release specification (including related substances) on vials selected from the sterilisation load. Sterility was tested on randomly selected vials. All results were within specification and little inter- or intra-batch variability was observed for any of the parameters.

During the validation process the effect of the sterilisation process on the product was also examined by conducting physical and chemical analysis pre and post sterilisation. This study demonstrated that all results remain within acceptable levels. No decrease in active substance content is observed. A commitment to perform validation on three full scale batches post authorisation to the same validation protocol is included in the dossier.

CONTROL OF STARTING MATERIALS

Active Substance

Active ingredients listed in a Pharmacopoeia.

Specification and routine tests for the active substance Meloxicam were described in detail. The active substance is monographed in the Ph. Eur. since January 2009 and the specifications provided by the applicant during the procedure comply with the Ph. Eur monograph.

Tests conducted on the active substance at the dosage form site on receipt using Ph Eur methodology are: identification, characters, related substance, loss on drying and assay.

Active ingredients not listed in a Pharmacopoeia.

Not Applicable

Physico-Chemical Characteristics liable to affect bioavailability

Meloxicam exists in five polymorphic forms I-V. These forms can be differentiated on the basis of their X-ray diffraction pattern and infrared absorption spectra. Full details were provided on the polymorphic form manufactured.

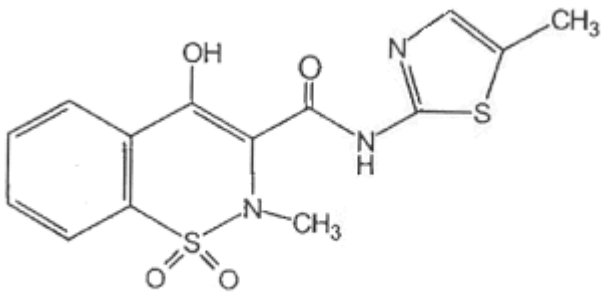
Scientific data

Nomenclature

International Non-proprietary Name (INN)	Meloxicam
IUPAC Name	4-hydroxy-2-methyl-N-(5-methyl-1,3-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1-1-dioxide
National Approved Names:	USAN: Meloxicam BAN: Meloxicam

CAS Number	[71125-38-7]
Synonyms and Abbreviations	None

Structural Formula



Molecular Formula	$C_{14}H_{13}N_3O_4S_2$
Molecular Weight	351.41

Description

Appearance	Pale yellow coloured powder
Boiling point	Not applicable (the compound is a solid)
pH	Not applicable
Water solubility	Insoluble
Solubility in Organic Solvents	Soluble in N,N-dimethylformamide Very slightly soluble in ethanol. Slightly soluble in acetone
Optical Rotation	Not applicable
Melting point	240-244°C with decomposition
Polymorphism	Forms I, II, III, IV and V

DMFs were provided which comply with the BP monograph. Various tests performed were described, including tests for starting material impurity, bulk density, particle size, residual solvents and assay. Analytical methods and validation were also described and these methods have been validated in line with VICH requirements.

Manufacturing description

A detailed description of the manufacturing process was provided, including time and temperature limits for specific reactions and reaction yields.

Quality control during manufacture

Details of quality control during manufacture were provided.

Development Chemistry

The structure has been shown analytically by UV, IR, MS, NMR, mass spectrum, elemental analysis, X-ray diffraction and FTIR. Satisfactory spectra and interpretation are provided. The route of synthesis also confirms the structure of meloxicam.

Physico-chemical characterisation: The solubility is described in the Ph. Eur. No literature describes isomerism for meloxicam.

The working standard was described and how it has been characterised.

Impurities

As well as the impurities listed in the Ph Eur monograph, the applicant has identified the starting material, Methyl benzothiazine isopropyl ester, as a potential impurity. This impurity is quantified using an in-house method and is limited on the specification. Actual levels of impurities detected in a number of production batches were detailed. Residual solvents used in the process were described and data presented for a number of production batches justifying the specification.

Batch analysis

Satisfactory batch data demonstrating compliance with the specification was provided for a number of batches.

Excipients

Specifications and routine tests

Excipients described in a Pharmacopoeia

Benzyl alcohol Ph. Eur.
Hydrochloric acid Ph. Eur.
Meglumine Ph. Eur.
Macrogol 400 Ph. Eur.
Macrogol 1500 Ph. Eur.
Sodium Chloride Ph. Eur.
Water for injections Ph. Eur.

Excipient(s) not described in a Pharmacopoeia

Not applicable.
Scientific data

All excipients comply with their Ph. Eur. monographs. Satisfactory 'typical' certificates of analysis were provided for all excipients.

Packaging Material (Immediate Packaging)

Specifications and routine tests

100 ml type I glass vial with a grey type I bromobutyl rubber stopper and aluminium cap.

Scientific data

The vials and closures comply with Ph. Eur. Requirements. Specifications, diagrammatic specifications and typical certificates of analysis were provided for all components. Fragmentation test was conducted in accordance with the Ph Eur test and results comply.

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

No materials of animal origin are used in the manufacture of this veterinary medicinal product.

CONTROL TESTS ON INTERMEDIATE PRODUCTS

Not applicable.

CONTROL TESTS ON FINISHED PRODUCT

Product Specification and Routine Tests:

Product specifications and tests for release at time of manufacture (general characteristics, specific standard)

Full details on finished product specification were provided, including characteristics, methods and acceptance limits.

Control methods

Descriptions of all tests listed on the specification were provided.

Safety tests

The sterility test is conducted by membrane filtration in accordance with Ph. Eur.

Scientific Data

Analytical validation of methods and comments on the choice of routine tests and standards

The method for determination of active, preservative and related substances has been validated in line with VICH requirements. The sterility test method has been validated in line with Ph.Eur. requirements and PIC/s recommendations. Other test methods are standard Ph. Eur. tests which do not require validation. Reference standards were also described.

Batch analyses

Batch analysis details were provided along with manufacturer's certificates of analysis for each of the pilot scale batches.

STABILITY

Stability Tests on the Active Substance

Data was provided on stability tests on the active substance. A commitment to conduct ongoing stability studies in accordance with the Ph. Eur. monograph and to report any out-of-specification results has been provided. The data support the proposed retest period although based on the data provided and with reference to EMEA/CVMP/422/99-Rev 3, no storage restriction is required.

Stability Tests on the Finished Product

Product Specification and Routine Tests for shelf life:

The shelf life specification is identical to that detailed at release. Related substances of meloxicam and benzyl alcohol do form part of the shelf life specification.

Stability Tests

Stability studies have been initiated on pilot scale batches and the relevant stability data was provided.

Results of tests

The data demonstrates the product to be extremely stable.

No significant change occurs over the course of the stability study to date under any of the storage conditions. Slight variability observed can be attributed to analytical variation rather than deterioration of the dosage form. In line with EMEA/CVMP/422/99-Rev 3, no storage precaution is therefore required.

The data presented supports a retest period of 24 months with no specific temperature precautions.
The photostability study shows increased levels impurities and changes in pH which demonstrate the need to protect the product from light. The freeze thaw cycle had no adverse effect on the product with all physical and chemical tests remaining within specification. No statement to protect from freezing is therefore required on the SPC or product literature.

A shelf life of 24 months with the following precautions was accepted

'Keep injection vial in the outer carton in order to protect from light'.

The applicant provided a commitment that the next three consecutive production-scale batches of finished product will be placed on stability, these studies will be finalised and the data provided to the competent authorities if outside of specifications or potentially outside specifications at the end of shelf life.

In-use Stability Tests

In use stability testing has been conducted on the pilot batches used in the stability study. Batches were 12 months old at the time of testing. Preservative efficacy testing and all parameters listed on the shelf life specification were determined following storage in an inverted position at 25˚C/60% RH. All results remain within specification and no adverse trends were observed for any of the parameters tested. The data supports an in-use shelf life of 28 days. A commitment was provided to repeat the in-use study with a batch approaching the end of shelf life.

OVERALL CONCLUSION ON QUALITY

The quality data is in accordance with current requirements. CVMP/VICH guidelines have been taken into account and no significant deviations from current guidelines have been identified. The quality of the product as described in the dossier is therefore acceptable.

3. SAFETY ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This marketing authorisation application for 'Melovem 5mg/ml Solution for Injection' is presented in accordance with Article 13(1) of Directive 2001/82/EC, as amended, which refers to applications for veterinary medicinal products which are generics of a reference medicinal product authorised within the Community. In accordance with this provision, the applicant states that 'Melovem 5mg/ml Solution for Injection' is a generic of 'Metacam 5 mg/ml Solution for Injection' (Boehringer Ingelheim Vetmedica GmbH).

In accordance with Article 13(2)(b) of the Directive, "generic medicinal product" shall mean a medicinal product which has:

a) the same qualitative and quantitative composition in terms of active principles

b) the same pharmaceutical form, and, where necessary,

c) bioequivalence of the two products has been demonstrated by appropriate bioavailability studies,

If the criteria detailed above are satisfied, the results of safety and residue tests or of pre-clinical and clinical trials are not required. Criteria (a) and (b) above have been satisfied and studies in support of bioequivalence in both target species have been presented.

SAFETY TESTING

Pharmacological Studies

The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC, as amended, (a generic application) and therefore data on pharmacodynamics are not required.

Pharmacodynamics

The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC, as amended, (a generic application). The reference product for this application is 'Metacam 5 mg/ml Solution for Injection' (Boehringer Ingelheim Vetmedica GmbH).

In support of this application, the Applicant has presented reports of two bioequivalence studies, one in pigs and one in cattle. While the stated reference product is 'Metacam 5 mg/ml Solution for Injection', the product used in the bioequivalence studies is 'Novem 5mg/ml Solution for Injection' (Boehringer Ingelheim Vetmedica GmbH). The product 'Novem 5mg/ml Solution for Injection' was the subject of an application for authorisation through the centralised procedure in accordance with Article 13.1.a(i) of Directive 2001/82/EC ('informed consent') and 'Metacam 5 mg/ml Solution for Injection' was the reference product. Given that 'Novem' was authorised on the basis of informed consent, 'Novem 5mg/ml Solution for Injection' and 'Metacam 5mg/ml Solution for Injection' can be considered the same. Consequently, it is accepted that the two products may be used interchangeably. The choice of reference product for the bioequivalence study was justified.

Pharmacokinetics

Pivotal Bioequivalence study in Pigs

Report Study Bioequivalence of Meloxicam administered as Novem 5 and a Dopharma test formulation to pigs

Details were provided of this comparative pharmacokinetic study performed in compliance with GLP to establish bioequivalence of a Dopharma test formulation (Melovem) and 'Novem 5 mg/ml Solution for Injection' after a single intramuscular administration to pigs. A two treatment, two period

crossover design with a wash out period of 48 hours was used. Twelve-week old clinically healthy pigs were used, and each animal received an intramuscular injection of 0.4 mg meloxicam/kg (equal to 2ml per 25 kg bodyweight) administered in the neck. Intravenous catheters were placed to facilitate sampling. Plasma samples were collected before and after administration of the products. Samples were frozen until analysed. Plasma samples were analysed for meloxicam content using a validated method. Quality control samples and calibration samples were prepared and run in conjunction with test samples.

The results were used to calculate C_{max}, T_{max}, AUC_{last} and AUC_{tot}. Calculated AUCs and measured C_{max} concentrations were dose normalised based on body weight, actual dose and content of active in the reference and test products. C_{max} and AUC values were analysed by ANOVA after log transformation. Upper and lower limits of the 90% confidence intervals were calculated with the estimated error variance found in the ANOVA tables. In the study protocol, the criteria for accepting bioequivalence were defined. The detailed results for the analysis of this study were provided.

Determination of Bioequivalence

The 90% confidence intervals for AUC and C_{max} fell within the specified limits which, in accordance with the EMEA/CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00) was considered demonstrative of bioequivalence. Based on the findings of the study, the test and reference products can be considered bioequivalent following administration to pigs.

Pivotal Bioequivalence study in Calves

Report Study Bioequivalence of Meloxicam administered as Novem 5 and a Dopharma test formulation to calves

A comparative pharmacokinetic study was performed to establish bioequivalence of a Dopharma test formulation ('Melovem', final formulation) and Novem 5 after a single subcutaneous administration of the products in the neck to calves. This study was conducted in accordance with GLP and involved a two treatment, two period crossover design with a between treatment wash out period of 21 days. 15 - 17 week old, clinically healthy calves were used and animals were acclimatised prior to commencement of the study. Each animal received a subcutaneous injection of 0.5 mg meloxicam/kg (equal to 10ml per 100 kg bodyweight) administered in the neck on one occasion. Plasma samples were collected before and at various time intervals after administration of the products and were analysed for meloxicam content using a validated method. Quality control samples and calibration samples were prepared and run in conjunction with test samples.

The results were used to calculate C_{max}, T_{max}, AUC_{last} and $T_{1/2}$. Calculated AUCs and measured C_{max} concentrations were dose normalised based on body weight, actual dose and content of active in the reference and test products. C_{max} and AUC values were analysed by ANOVA after log transformation. Upper and lower limits of the 90% confidence intervals were calculated with the estimated error variance found in the ANOVA tables. In the study protocol, the criteria for accepting bioequivalence were defined. The detailed results for the analysis of this study were provided.

Determination of Bioequivalence

The 90% confidence intervals for AUC and C_{max} fell within the specified limits, which, in accordance with the EMEA/CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00) can be considered demonstrative of bioequivalence. Based on the findings of the study, the test and reference products can be considered bioequivalent following administration to cattle.

Validation of the analytical method for the determination of Meloxicam in bovine and porcine plasma

The validation study was conducted to GLP. Based on the findings of this study, it is accepted that the method was adequate for the determination of meloxicam in bovine and porcine plasma.

Tolerance in the target species of animal

Tolerance studies have been provided following administration of the product to cattle and pigs.

Studies on metabolites, impurities, other substances and formulation

All the excipients present in 'Melovem 5mg/ml Solution for Injection' can be considered well established and have an extensive history of use in human and veterinary medicinal products and their presence in 'Melovem 5mg/ml Solution for Injection' is not considered to present an increased risk to the user.

The product composition was detailed. It is accepted that all excipients have a history of use in human and veterinary pharmaceutical products. It is noted that all excipients are either included in Annex II of Council Regulation 2377/90 or are considered outside the scope of that Regulation.

User Safety

User safety was addressed in the dossier.

Inherent Toxicity

'Melovem 5mg/ml Solution for Injection' is bioequivalent to 'Metacam 5mg/ml Solution for Injection'. There will be no difference between the products in respect of inherent toxicity.

Exposure of the user

'Melovem 5mg/ml Solution for Injection' will be used in the same way as the reference product and therefore the potential for exposure of the user to the product will be the same as for the reference product.

Conclusion including the risk management proposals

The warnings and precautions as listed in the product literature of the reference product can be applied to 'Melovem 5mg/ml Solution for Injection'. The following user warnings are proposed:

- Accidental self-injection may give rise to pain. People with known hypersensitivity to NSAIDs should avoid contact with the veterinary medicinal product.

- In case of accidental self-injection, seek medical advice immediately and show the package leaflet or label to the physician.

Given that:

- bioequivalence with 'Metacam 5mg/ml Solution for Injection' is demonstrated,
- the excipients included in the formulations can be considered safe, and
- the posology and indications are identical to those of the reference product (with the exception that the reference product is also authorised for use by the intravenous route in cattle),

it is accepted that the potential hazard to the user posed by 'Melovem 5mg/ml Solution for Injection' will not be any greater than that posed by the reference product. The proposed user safety statements are considered appropriate.

Environmental Risk Assessment

Phase I Assessment

'Melovem 5mg/ml Solution for Injection' is intended for use in pigs and cattle as follows:

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.

In conducting the Phase I assessment, the Applicant has referred to the VICH Guideline on Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products-Phase I and the decision tree therein. Based on the answer to question number 5, the Applicant has concluded that the EIA may be stopped at that point and that there is no requirement for a Phase II assessment.

Question 5 of the decision tree asks 'Will the VMP be used to treat a small number of animals in a flock or herd?'. In accordance with the CVMP Guideline on EIAs for veterinary medicinal products in support of the VICH guidelines GL6 and GL38, it is stated that injectable NSAIDs can be considered as being used for treatment of 'a small number of animals'.

It is noted that the product is indicated in cattle for the treatment of acute respiratory infections and that such disease conditions might be expected to involve several animals in a herd. However, as the product is indicated for use with appropriate antibiotic therapy, it can be accepted that not all animals administered an antibiotic for acute respiratory infection will be administered the product. Therefore it is considered that the indications for use of the product will result in the product being used to treat a 'small number of animals' and it is accepted that the ERA can be concluded at question 5.

Phase II Assessment

No data were presented as the Phase I assessment concluded that there was no requirement for a Phase II assessment.

Impact assessment and specific provisions to limit it, as appropriate (article 12(3)(j))

Given that the environmental risk assessment can be stopped at Phase I, it is concluded that the product, when used as recommended, will not pose a risk to the environment.

Conclusion on Part III.A.

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (a generic application). *In vivo* data provided in support of the application demonstrate that the test product 'Melovem 5mg/ml Solution for Injection' is bioequivalent to the reference product 'Novem 5mg/ml Solution for Injection'. 'Novem 5mg/ml Solution for Injection' and 'Metacam 5mg/ml Solution for Injection' can be considered the same product. The product when used in accordance with label recommendations is not expected to represent a hazard to the user or to the environment.

RESIDUE DOCUMENTATION

The present application is submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended, which refers to applications for veterinary medicinal products which are generics of a reference medicinal product authorised within the Community. In accordance with this provision, the applicant states that 'Melovem 5mg/ml Solution for Injection' is a generic of 'Metacam 5 mg/ml Solution for Injection' (Boehringer Ingelheim Vetmedica GmbH).

Precise identification of the product concerned by the application

Formulation used in the residue studies (related to the formulation of the final product)

The formulation used in the residue depletion studies was detailed.

Residue studies

Depletion of residues

The Applicant provided reports of residue depletion studies conducted in both pigs and cattle. These are described below. In the studies conducted, depletion of residues at the injection site only was evaluated. Given that bioequivalence is claimed, it is assumed that depletion of resides from target tissues (muscle, liver and kidney) should occur at a similar rate for both test and reference products. Consequently, it is assumed that for those tissues, the withdrawal period of the reference product can be applied to the test product. However, given that the present application relates to a product that is to be administered by the intramuscular route (pigs) and the subcutaneous route (cattle), it is required that, in addition to bioequivalence studies, equivalent (or faster) depletion of residue from the injection site should be demonstrated (EMEA/CVMP/036/95-FINAL).

Pivotal residue depletion study in Pigs

Report Study Residues in Pigs; confirmation of withdrawal period after intramuscular administration of Meloxicam 0.5% Inj.

This residue depletion study to determine residues of meloxicam at the injection site following intra-muscular administration of the test article to pigs was conducted in accordance with GLP. Clinically healthy pigs aged approximately 14 weeks old were administered 0.4mg of meloxicam/kg bodyweight (equal to 2ml per 25kg bodyweight) by intramuscular injection in the neck on two occasions with a between-treatment interval of 24 hours. The first injection was administered to the right side and the second injection to the left side of the neck. Blood samples were taken before first administration of the product and after administration and again just before slaughter.

Plasma was stored frozen pending analysis. Animals were slaughtered on day 5, day 7 and day 9 after the final administration of the product. Core injection site and surrounding tissue samples were harvested and homogenised. Tissue samples were stored frozen pending analysis. Tissue samples (core and surround tissue from both injection sites) were analysed for meloxicam using a validated method. Quality control samples and calibration samples were prepared, stored with the test samples and, subsequently, were run in conjunction with test samples. In plasma, meloxicam was not detected in pre-dose and pre-slaughter samples. At the three sampling time points on the day of product administration, meloxicam was detected in plasma, with peak concentrations ranging from 0.60 to 1.57 µg/ml at one hour post-injection. Tissue concentrations of meloxicam were below the limit of quantification (10µg/kg) in samples from all animals at each of the sampling times of 5 days, 7 days and 9 days post injection.

Meloxicam residues were determined to be below the MRL for muscle (20µg/kg) in all injection site samples five days after administration of the test item. While it is noted that no animals were slaughtered before the proposed withdrawal period of 5 days, the design of the study was considered

sufficient to confirm, relevant to the reference product, equivalent depletion of residue from the injection site.

The product was administered in accordance with the proposed posology. In the study report, the test product is referred to as 'Meloxicam 0.5% Inj.'. The Applicant confirmed that the product used in the residue depletion study was the same as the formulation proposed to be marketed.

Residues of meloxicam at the injection site were determined to be below the LOQ (10 µg/kg) which is less than half the established MRL for meloxicam in porcine muscle. The results of the analysis of the plasma samples taken pre- and post-treatment confirmed that test animals were exposed to the test product during the study. Based on these data, it is concluded that the Applicant satisfactorily demonstrated the appropriateness of the proposed withdrawal period of 5 days (the same as that authorised for the reference product 'Metacam 5mg/ml Solution for Injection') when the product is used in pigs (maximum injection volume ~ 4 ml).

In addition to the pivotal residue depletion study described above, the Applicant provided a report of a single time point residue depletion study conducted in heavier pigs (mean bodyweight of 103 Kg) in order to confirm that the voilume of test product administered at a single injection site does not impact on the proposed withdrawal period. The product was administered by the proposed route of administration (intramuscularly), at the proposed dosage of 0.4 mg/Kg bodyweight and for the maximum proposed duration (daily for two days). The second injection was administered on the opposite side of the neck to where the first injection was admninistered in line with advice on correct administration of the product as detailed in section 4.9 of the SPC. Total volumes of product administered at each injection site were approximately 8 ml.

At five days after treatment, residue concentrations in all injection site tissue samples were found to be below the LOQ of the assay (8.6732 ng/g) and therefore were below the muscle MRL of meloxicam of 20 µg/Kg by more than a factor of two. Therefore, it can be accepted that a withdrawal period of five days is adequate to ensure consumer safety when the product is administered to pigs weighing up to 100 Kg bodyweight.

In view of the findings of both residue studies, it is accepted that a withdrawal period of 5 days is appropriate for all weight ranges of pigs. Further, it is accepted that a restriction on the volume of product to be administered at a single site is not required.

The analytical methods for determination of meloxicam were satisfactorily validated. Further, quality control samples analysed in conjunction with test samples confirm satisfactory performance of the method.

Pivotal residue depletion study in Cattle

Report Study Residues in Cows; confirmation of withdrawal period after subcutaneous administration of Meloxicam 0.5% Inj.

This residue depletion study to determine residues of meloxicam at the injection site following subcutaneous administration of the test article to cattle was conducted in accordance with GLP. Clinically healthy cows were administered 0.5mg of meloxicam/kg bodyweight (equal to 10ml per 100kg bodyweight) by subcutaneous injection in the neck on a single occasion. The injection was administered to the left side of the neck. Actual dose of product administered ranged from 49 to 58 ml per animal. Blood samples were taken before the administration of the product and after administration and again just before slaughter. Plasma was stored frozen pending analysis. Animals were slaughtered in groups on day 15 and day 18 after administration of the product. Core injection site and surrounding tissue samples were harvested and homogenised. Tissue samples were stored frozen pending analysis. Tissue samples (core and surround tissue from both injection sites) were analysed for meloxicam using a validated method. Quality control samples and calibration samples were prepared, stored with the test samples and, subsequently, were run in conjunction with test samples. In plasma, meloxicam was not detected in pre-dose and pre-slaughter samples. At the three

sampling time points on the day of product administration, meloxicam was detected in plasma, with peak concentrations ranging from 1.09 to 2.26 µg/ml at eight hours post-injection. Tissue concentrations of meloxicam were below the limit of quantification (10µg/kg) in samples from all animals at each of the sampling times of 15 days and 18 days post treatment. Meloxicam residues were determined to be below the MRL for muscle (20µg/kg) in all injection site samples fifteen days after administration of the test item. The design of the study was considered sufficient to confirm, relevant to the reference product, equivalent depletion of residue from the injection site. Tissue sampling was in line with the guidance in EMEA/CVMP/542/03 (Guideline on Injection Site Residues).

The product was administered in accordance with the proposed posology. It would appear that volumes of test product ranging from 49-58 ml were administered to the test animals at a single site. This can be considered a worse case for injection site residues. In the study report, the test product is referred to as 'Meloxicam 0.5% Inj.'. The Applicant confirmed that the product used in the residue depletion study was the same as the formulation proposed to be marketed.

Residues of meloxicam at injection site were determined to be below the LOQ (10 µg/kg) which is less than half the established MRL for meloxicam in bovine muscle. The results of the analysis of the plasma samples taken pre- and post-treatment confirmed that test animals were exposed to the test product during the study. Based on these data, the Applicant has satisfactorily demonstrated the appropriateness of the proposed withdrawal period of 15 days (the same as that authorised for the reference product 'Metacam 5mg/ml Solution for Injection') when the product is administered by the subcutaneous route to cattle. The analytical methods for determination of meloxicam were satisfactorily validated. Further, quality control samples analysed in conjunction with test samples confirm satisfactory performance of the method.

MRLs

The MRLs for meloxicam in porcine and bovine animals have been established by the CVMP and are included in Annex I of EU Regulation 2377/90 as follows:

Pharmacologically active substance	**Marker Residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**
Meloxicam	Meloxicam	Porcine	20µg/kg 65µg/kg 65µg/kg	Muscle Liver Kidney	
Meloxicam	Meloxicam	Bovine	20µg/kg 65µg/kg 65µg/kg	Muscle Liver Kidney	

All excipients have a history of use in human and/or veterinary pharmaceutical products. It is noted that all excipients are either included in Annex II of Council Regulation 2377/90 or are considered outside the scope of that Regulation.

Withdrawal periods

The Applicant proposed the following withdrawal periods:

Cattle: 15 days.
Pigs: 5 days.

Based on the results of the residue depletion studies provided, the proposed withdrawal periods for the product are appropriate:

- Given that bioequivalence is claimed, it is assumed that depletion of resides from target tissues (muscle, liver and kidney) should occur at a similar rate for both test and reference products. Consequently, it is assumed that for those tissues, the withdrawal period of the reference product can be applied to the test product.

- The results of the residue studies detailed above have demonstrated that the concentrations of meloxicam at the injection site are below the MRL (20µg/kg) of muscle tissue in both species at the proposed withdrawal periods of 5 days and 15 days for pigs and cattle, respectively.

Analytical method(s)

Description

The Applicant provided details of the method used for the analysis of meloxicam in bovine and porcine tissue.

Validation of the method

The Applicant provided information on the validation of the analytical method used for the analysis of meloxicam in muscle tissue samples harvested from cattle and pigs. The validation study was conducted to GLP. Based on the findings of this study, it is accepted that the method is adequate for the determination of meloxicam in bovine and porcine muscle.

Conclusion on the Residue Part

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (a generic application). Given that bioequivalence is claimed, it is assumed that depletion of resides from target tissues (muscle, liver and kidney) should occur at a similar rate for both test and reference products. Consequently, it is assumed that for those tissues, the withdrawal period of the reference product can be applied to the test product. However, given that the present application relates to a product that is to be administered by the intramuscular route (pigs) and the subcutaneous route (cattle), it is required that, in addition to bioequivalence studies, equivalent (or faster) depletion of residue from the injection site should be demonstrated (EMEA/CVMP/036/95-FINAL). The Applicant provided reports of residue depletion studies conducted in both pigs and cattle. In the studies conducted, depletion of residues at the injection site only was evaluated. The results of both studies have demonstrated that the concentrations of meloxicam at the injection site are below the MRL (20µg/kg) of muscle tissue in both species at the proposed withdrawal periods of 5 days and 15 days for pigs and cattle, respectively. The product is not permitted for use in lactating animals producing milk for human consumption. The analytical methods for determination of meloxicam were satisfactorily validated.

4. CLINICAL ASSESSMENT (EFFICACY)

PRECLINICAL STUDIES

This marketing authorisation application for 'Melovem 5mg/ml Solution for Injection' is presented in accordance with Article 13(1) of Directive 2001/82/EC, as amended, which refers to applications for veterinary medicinal products which are generics of a reference medicinal product authorised within the Community. In accordance with this provision, the applicant states that 'Melovem 5mg/ml Solution for Injection' is a generic of 'Metacam 5 mg/ml Solution for Injection' (Boehringer Ingelheim Vetmedica GmbH). The European Commission issued a Community marketing authorisation for the reference product on 7th January 1998. In accordance with Article 13(2)(b) of the Directive, "generic medicinal product" shall mean a medicinal product which has:

d) the same qualitative and quantitative composition in terms of active principles

e) the same pharmaceutical form, and, where necessary,

f) bioequivalence of the two products has been demonstrated by appropriate bioavailability studies,

If the criteria detailed above are satisfied, the results of safety and residue tests or of pre-clinical and clinical trials are not required. Criteria (a) and (b) above have been satisfied. Studies in support of

bioequivalence in both target species have been presented and are considered acceptable. CVMP concludes that bioequivalence of the two products has been demonstrated.

Tolerance in the target species of animal

For a generic product, it is generally accepted that data on the systemic tolerance of the product in the target species is not required. However, for injectable products, data to confirm acceptable local tolerance in target species should be provided. The Applicant provided the results of local tolerance studies in cattle and pigs following the administration of the product to those species. These studies are described below.

Pivotal Tolerance study in Pigs

Report Study Meloxicam 0.5% Injection after intramuscular administration to pigs

This study to evaluate local tolerance to Melovem (Meloxicam 0.5%) following intramuscular injection in pigs was conducted in accordance with GLP (with the exception of blood samples and pathological/histopathological examinations). Clinically healthy pigs 11 weeks of age were selected and acclimatised. Intravenous catheters were placed to facilitate blood sampling. The study animals were randomly divided into two groups (A & B). The examiner was blinded to the administration of the test (Melovem) and control (physiological saline) articles to facilitate unbiased assessment of tissue reactions. On Day 1, 0.4 mg meloxicam /kg bodyweight (equal to 2ml of the test product 'Melovem' per 25 kg bodyweight) was administered to animals in group A. The animals in group B were administered saline at doses of 2ml per 25 kg bodyweight. All injections were administered by the intramuscular route in the left side of the neck. Immediately before administration, and at various time intervals after administration, injection sites were examined by inspection, palpation and were assessed for appearance (size), inflammation (painfulness and warmth), oedema or other changes noted. Details were provided of the scoring system used.

Blood samples were collected for the determination of creatinine phosphokinase (CPK) and aspartate transaminase (AST) before and at various time intervals after administration of the products. Samples were stored under a controlled temperature until analysed. Two days after test product administration, animals from both groups (equal numbers of both sexes) were slaughtered. Prior to slaughter, blood samples were collected for CPK and AST determination. Five days after test product administration, the remaining animals were slaughtered. Prior to slaughter, blood samples were collected for CPK and AST determination. Injection sites were examined histologically. Injection site scores were analysed using ANOVA. CPK and AST concentrations were analysed using Student's *t*-test. For all tests, $p<0.05$ was considered to be significant.

The results for the analysis of the study were detailed. Two out of eight animals receiving the test product displayed swelling at the injection site at one hour post injection measuring 20cm² and 16cm². From 2 hours post injection the swellings were no longer visible. No placebo treated animals displayed swellings at the injection site. None of the injection sites in either group were recorded as being painful or warm. No significant differences between groups were detected for the parameters CPK or AST. The results for histological analysis were provided. The Applicant concluded that only small acceptable differences were noted for the test product in respect of injection site swelling when compared to the placebo treated group. No statistically significant effects were found. The Applicant also concluded that administration of the test product only caused slight and expected pathological changes.

The Applicant provided results of a study conducted to GLP standards. The study investigated local tolerance only. As stated previously, for a generic product, it is generally accepted that data on the systemic tolerance of the product in the target species is not required. In the present study, the test product was administered on a single occasion only; however, the recommended dosing regime is for two injections with an inter-dose interval of 24 hours. Although the product was not administered in accordance with the recommended posology, it can be considered adequate for the evaluation of local tolerance. In practice one would expect that every reasonable effort would be made to ensure that a second injection would be administered at a different site to the first and this is also required in the

SPC. The GLP-study was adequately designed and presented. Various parameters were assessed and gave a thorough picture of the local tolerance.

It is noted that one of the animals treated with the test product was recorded as having an elevated AST level of 53U/L at 30 hours which subsequently was recorded as 37 U/L at 48 hours and then 41 U/L at 72 hours. The AST level for this animal was 41 U/L at the start of the study. The Applicant indicated that the laboratory reference for this biochemical parameter is 20 – 35U/L. The laboratory advised that values >35 U/L and up to 50 U/L must be regarded as 'normal' caused by a 'physiologically high load on the liver' and that values > 50 U/L are indicative of 'pathological deviation of the liver'. Given the modest nature of the increase in this parameter, the fact that the parameter is not consistently elevated and the fact that the animal in question appeared clinically normal, it is concluded that the temporary increase in this parameter was of no clinical significance and was not likely to be product related. Notwithstanding the conclusion with respect to this specific occurrence, it is acknowledged that NSAIDs may have an effect on hepatic function and it is noted that section 4.3 of the proposed SPC contra-indicates the use of the product in animals suffering from impaired hepatic function.

On the basis of the injection site scores, it is evident that a small (up to 20cm² in diameter), non-painful and temporary swelling may result at the site of injection in some animals. It would appear that the swelling is of a transient nature and was recorded as having disappeared by 2 hours post injection. The pathological changes observed would appear to be expected and acceptable changes following intramuscular administration. Given the very transient nature of the swelling and the mild severity of the pathological change, it is accepted that the product is well tolerated locally, at the injection site, following intramuscular administration to pigs. The following statement is however included in Section 4.6 (Adverse reactions (frequency and seriousness)) of the SPC:
'Transient swelling at the injection site was observed in clinical studies following intramuscular administration in pigs.'

The absence of data on systemic tolerance is accepted.

Pivotal Tolerance study in Cattle

Report Study Meloxicam 0.5% Injection after subcutaneous administration to cows

This study to evaluate local tolerance to Melovem (Meloxicam 0.5%) following subcutaneous injection to cows was conducted in accordance with GLP (with the exception of blood samples and pathological/histopathological examinations). The control article was physiological saline. Clinically healthy dairy cows in the age range 2.5 – 7.5 years of age were acclimatised and were randomly divided into two groups (A & B).

The examiner was blinded to the administration of the test and control articles to facilitate unbiased assessment of injection site reactions. On Day 1, 0.5 mg meloxicam/kg bodyweight (equal to 10 ml of the test product 'Melovem' per 100 kg bodyweight) was administered to animals in group A. The animals in group B were administered saline at doses of 10 ml per 100 kg bodyweight. All injections were administered by the subcutaneous route in the left side of the neck. Immediately before product administration and at various time intervals after administration, injection sites were examined by inspection, palpation and were assessed for appearance (size), inflammation (painfulness and warmth), oedema or other changes noted. Details were provided of the scoring system used.

Blood samples were collected for the determination of creatinine phosphokinase (CPK) and aspartate transaminase (AST) before and at various time intervals after administration of the products. Samples were stored at a controlled temperature until analysed. Seven days after test product administration, animals from each group were slaughtered. Prior to slaughter, blood samples were collected for CPK and AST determination. Fifteen days after test product administration, the remaining animals were slaughtered. Prior to slaughter, blood samples were collected for CPK and AST determination. Injection sites were examined histologically.

Injection site scores were analysed using ANOVA. CPK and AST concentrations were analysed using Student's t-test. For all tests, $p<0.05$ was considered to be significant. The results for the analysis of this study were detailed. One hour post injection, animals receiving the test product had injection sites recorded as 'slightly' to 'clearly' swollen whereas those animals receiving the placebo had injection sites recorded as slightly swollen. From 24 hours, no differences between groups were recorded. Pain on palpation was detected in one animal in the test product group and one in the placebo group following injection. The injection site was more painful and pain lasted longer (up to 6 hours) for the animal in the test product group. No significant differences between groups were detected for CPK and AST. At seven days after injection, only minor pathological/small localised histopthological deviations were observed in the injection sites of the test product group and no pathological/histopathological deviations were observed in injection site samples for the placebo group. At 15 days, a decrease in incidence of deviations was detected. The results for histological analysis were provided.

The Applicant concluded that only small acceptable differences were noted for the test product in respect of injection site swelling when compared to the placebo treated group. The Applicant also concluded that administration of the test product only caused slight and expected pathological changes. The study was conducted to GLP standards and investigated local tolerance only. The design of the study was considered adequate for this purpose. As stated previously, for a generic product, it is generally accepted that data on the systemic tolerance of the product in the target species is not required. The GLP-study was adequately designed and presented. Various parameters were assessed and gave a thorough picture of the local tolerance.

On the basis of the injection site scores, it is evident that transient, non-painful swelling may result at the site of injection in some animals. The method of scoring used in this study results in statistically non-significant differences being obtained for swelling despite the fact that maximal swellings of up to 80cm² (one subject at 1 hour post administration) were observed in cows administered the test product. While it is acknowledged that there was no difference in swellings between the two groups after 24 hours post injection, seven out of eight animals administered the test product experienced swelling at the injection site for a short time after injection. It is noted that the SPC of the reference product 'Metacam 5mg/ml Solution for Injection' contains information relating to the potential for transient injection site reactions following subcutaneous administration of the reference product to cattle. Given the findings of the above study, it is accepted that the product is reasonably well tolerated, but considered appropriate that a similar statement should be included in the proposed SPC for 'Melovem 5mg/ml Solution for Injection'.

The following statement is included in Section 4.6 (Adverse reactions (frequency and seriousness)) of the SPC:
'Transient swelling at the injection site was commonly reported in clinical studies following subcutaneous administration in cattle. Injection site swelling may be painful.'

The absence of data on systemic tolerance is accepted.

Preclinical studies

In accordance with Article 13(1) of Directive 2001/82/EC, as amended, which refers to applications for veterinary medicinal products which are generics of a reference medicinal product authorised within the Community, the Applicant is not required to provide the results of safety and residue tests or of pre-clinical and clinical trials if he can demonstrate that the medicinal product is a generic of the reference medicinal product. No preclinical studies have been provided in accordance with the legal basis for this application as outlined above.

CLINICAL STUDIES

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (a generic application). *In vivo* data provided in support of the application demonstrate that the test product 'Melovem 5mg/ml Solution for Injection' is bioequivalent to the reference product 'Novem 5mg/ml Solution for Injection'. 'Novem 5mg/ml Solution for Injection' and 'Metacam 5mg/ml Solution for Injection' can be considered the same product. Since it is accepted that the products are bioequivalent, it can be concluded that the systemic effects of the two products in respect of efficacy will be the same.

Overall, the tolerance of the product was acceptable in both cattle administered the product by the subcutaneous route and in pigs administered the product by the intramuscular route. Transient swelling was a feature of test product administration in both target species and the potential for this effect is reflected in the SPC.

5. BENEFIT RISK BALANCE

The application for Melovem concerns a generic medicinal product as defined in Article 13(2)(b) of Directive 2001/82/EC, as amended by Directive 2004/28/EC, and refers to a reference veterinary medicinal product with a Marketing Authorisation granted in the Community. The chosen reference veterinary medicinal product is Metacam 5 mg/ml solution for injection for cattle and pigs

Melovem solution for injection for cattle and pigs is indicated in cattle for subcutaneous use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle and for use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over 1 week of age and young, non-lactating cattle, and in pigs for intramuscular use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation.

Melovem is presented in a cardboard box with 1 colourless, type I glass injection vial of 100 ml, which is closed with a bromobutyl rubber stopper and sealed with an aluminium cap. Melovem contains meloxicam at a concentration of 5 mg/ml. 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 *E. coli* endotoxin administration in calves and pigs.

The quality data provided are in accordance with current requirements. Data provided in support of the application demonstrate that Melovem 5mg/ml Solution for Injection is bioequivalent to the reference product. Since it is accepted that the products are bioequivalent, it can be concluded that the systemic effects of the two products in respect of safety and efficacy will be the same.

The product when used in accordance with label recommendations is not expected to represent a hazard to the user or to the environment. Furthermore, the proposed withdrawal periods are in line with those of the reference product and are considered appropriate.

The benefits of Melovem in are cattle the reduction of clinical signs in acute respiratory infection when used with appropriate antibiotic therapy and the reduction of clinical signs in calves of over 1 week of age and young, non-lactating cattle when used in cases of diarrhoea in combination with oral re-hydration therapy. The benefits in pigs are reduction of the symptoms of lameness and inflammation in non-infectious locomotor disorders.

As stated above, given that bioequivalence is accepted, the efficacy profile of the test products will be the same as that of the respective reference products: The indications and posology as authorised for the reference products can be applied to the test product. Overall, the tolerance of the product was acceptable in both cattle administered the product by the subcutaneous route and in pigs administered the product by the intramuscular route. Transient swelling was a feature of test product administration in both target species and the potential for this effect is reflected in the SPC.

The CVMP, on the basis of quality, safety and efficacy data submitted, considers that there is a favourable benefit to risk balance for Melovem and therefore recommends the granting of the marketing authorisation. The benefit: risk assessment is positive.

Based on the data presented, the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product was considered to be in accordance with Directive 2001/82/EC as amended.