SCIENTIFIC DISCUSSION

1. SUMMARY OF THE DOSSIER

The application concerns Meloxivet, a generic medicinal product as defined in Article 13(2)(b) of Directive 2001/82/EC, as amended by Directive 2004/28/EC. The reference veterinary medicinal product is Metacam 1.5 mg/ml oral suspension for dogs, a product with a Community Marketing Authorisation and originally authorised in Germany in 1992.

The active substance is meloxicam, a non-steroidal anti-inflammatory drug belonging to the acidic enolcarboxamide (oxicam) class. *In vitro*, meloxicam is preferentially active against cyclooxygenase-2. The recommended posology consists of an initial single dose of 0.2 mg meloxicam/kg body weight on the first day, followed by once daily administration (24-hour intervals) of 0.1 mg meloxicam/kg body weight. The product is to be administered mixed with food.

According to the legislation, the Applicant is not required to provide the results of the safety and residue tests or of the pre-clinical and clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product for which the data exclusivity period has expired.

2. QUALITY ASSESSMENT

Composition

Qualitative Composition	Quantitative composition mg/ml		Function	Reference to analytical quality
	0.5 mg/ml suspension	1.5 mg/ml suspension		
Active Substance				
Meloxicam	0.5	1.5	Active substance	British Pharmacopoeia (BP)*
Other ingredients				
Microcrystalline cellulose and carboxymethylcellulose sodium (Dispersible cellulose)				BP
Xanthan gum				Ph.Eur.
Sodium benzoate	1	1		Ph.Eur.
Sodium saccharin				Ph.Eur.
Glycerol				Ph.Eur.
Sorbitol				Ph.Eur.
Citric acid monohydrate				Ph.Eur.
Sodium hydroxide				Ph.Eur.
Purified water				Ph.Eur.

* Additional company specification for particle size is also applied.

Container

Product strength	Container Sizes	Description	Dosing device	Closure
0.5 mg/ml	10 ml 30 ml	Type III Ph. Eur. Amber glass bottle	3 ml graduated in BW divided by kg corresponding to the maintenance dose.	10 ml: Child proof HDPE with LDPE insert 30 and 150 ml: Child proof PP and HDPE liner with LDPE insert
1.5 mg/ml	10 ml 30 ml 150 ml			

The dosing syringe is delivered together with the bottle in the carton box. There are two syringes, an amber syringe for the 0.5 mg/ml presentation and a clear syringe for the 1.5 mg/ml presentation.

Development Pharmaceutics

Meloxivet has been formulated to be essentially similar to the reference product Metacam 1.5 mg/ml oral suspension. The product contains Meloxicam at a concentration of 0.5 or 1.5 mg/ml presented as oral suspensions. Bioequivalence between the 1.5 mg/ml strength and the reference product is discussed in Part III. Extrapolation of this bioequivalence to the 0.5 mg/ml formulation has been accepted based on comparative *in vitro* dissolution between the 0.5 mg/ml and 1.5 mg/ml formulations. All formulation development work has been conducted on the 1.5 mg/ml formulation. Correlation/extrapolation to the 0.5 mg/ml formulation has been demonstrated with data provided to establish equivalent sedimentation rates and dissolution profiles for the two formulation strengths. Results from stability studies demonstrate equivalent resuspendability, viscosity, yield profile and particle size for the two formulations up to 12 months storage. The equivalence of the rheological properties of the two formulations has been adequately demonstrated.

Physico-chemical characteristics which may affect rheological properties such as density, pH, suspension particle size and zeta potential were examined throughout development. pH is buffered with citric acid and adjusted with sodium hydroxide. The product has also been formulated to contain the preservative sodium benzoate at a concentration of 1.0 mg/ml. This is the same preservative system used in the reference product. Preservative efficacy has been demonstrated for three freshly manufactured batches of each strength. In each case compliance with Ph. Eur. 5.1.3 criteria for oral preparations is demonstrated. Compliance with Ph. Eur. 5.1.3 criteria for oral preparations was demonstrated (including *E. coli*).

Dissolution studies were carried out in order to determine the effect of particle size. Various media with and without surfactants were investigated and media were selected which gave sink conditions with a factor of 3 to 5 relative to active substance solubility. Dissolution studies using active substance, formulations manufactured with unmilled and milled active substance and comparisons with the reference product which lead to the establishment of the appropriate particle size to achieve bioequivalence with the reference product were described.

The packaging components chosen are commonly used for pharmaceutical products. Amber glass was justified with reference to a light sensitivity study which demonstrated that the formulated product is sensitive to light. The study was carried out in line with VICH requirements and degradation of the active substance and the preservative was observed following exposure to light. The stability data and in-use stability data provided, demonstrated the compatibility of the product and container. Dose accuracy demonstrating compliance with Ph. Eur. 2.9.27 (uniformity of mass of delivered dose from multidose containers), was reported with results for 20 determinations of the expelled weight for all markings on both syringes provided.

Method of manufacture

Manufacturing Formula and Batch Size

0.5 mg/ml:
The manufacturing formulae for the proposed batch sizes of 500 L and 3,000 L were provided.

1.5 mg/ml:
The manufacturing formula for the proposed batch size of 3,000 L was provided.

No adjustment was made for active substance potency and no overages were used in the formulation.

Manufacturing Process and In-process Controls

A flow chart of the manufacturing process for the 0.5 mg/ml suspension and the in-process controls (IPC's) were provided. The process is identical for the 1.5 mg/ml solution. A detailed description of each operation step in the manufacturing process was submitted.

The manufacturing process and in-process controls are described appropriately and are considered adequate.

Validation of Manufacturing Process

Based on the manufacturers experience in the manufacture of this type of dosage form, the process can be considered to be a standard one for the proposed manufacturer. Process validation protocols were provided for 3,000 and 500 litre batches of the 1.5 mg/ml and 0.5 mg/ml strengths. The protocols addressed satisfactorily critical aspects of the manufacturing process

CONTROL OF STARTING MATERIALS

Active Substance

Specification and routine tests
Active ingredients listed in a Pharmacopoeia.

Meloxicam (British Pharmacopeia (BP))
A Drug Master File (DMF) from the active substance manufacturer was provided. In addition to the BP monograph a draft monograph for meloxicam has been published in Pharmeuropa 18.3. There are minor differences between the BP and Pharmeuropa monographs. The specification provided in the DMF complies with the BP monograph. Additional in-house tests are also included. Polymorphic form was included on the specification, as a non- routine test. X-ray diffraction data presented for 12 month old batches demonstrated that there is no change in polymorphic form of the active substance following manufacture or storage of the dosage form.

Analytical methods and validation
The assay of meloxicam is by non-aqueous titration and related substances are determined by the methods described in the BP monograph and therefore are considered validated. Additional in-house methods were described. These methods were validated in line with VICH requirements.

Physico-Chemical Characteristics liable to affect bioavailability

Meloxicam exists in five polymorphic forms I-V. The active substance supplier routinely manufactures polymorphic form I as evidenced by X-ray diffraction and IR spectra with reference to published spectra. Spectral data confirming this were presented and a test for polymorphic form is included as a non routine test on the specification. Particle size was limited on the active substance specification.

C.1.2 Scientific data

The active substance derives from one manufacturer.

1.2.1. Nomenclature

Nomenclature
Nomenclature of the active substance is presented
Generic names: Meloxicam (INN, BAN)
Chemical name: 4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide
Other name: 2H-1,2-benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-1,1-dioxide
CAS no. 71125-38-7
Description
Description of the active substance
Description: Pastel yellow powder
Molecular formula: C14H13N3O4S2
Molecular weight: 351.4

Manufacturing description

Isopropyl-4-hydroxy-2-methyl-2-benzothiazine-3-carboxylate-1,1-dioxide
(Methyl benzothiazine isopropyl ester) is reacted with 2-amino-5- methylthiazole in a suitable solvent to give crude meloxicam which is purified to produce meloxicam.

Quality control during manufacture

Appropriate quality control is carried out.

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 were provided. The route of synthesis also confirmed the structure of meloxicam.

Physico-chemical characterisation

The solubility is described in the British Pharmacopoeia monograph. No literature describes isomerism for meloxicam. The working standard is obtained from a commercial batch and has been characterised with the BP Certified Reference Standards (CRS). Meloxicam impurity standards, BP CRS material are used as reference standards.

Impurities

As well as the impurities listed in the BP monograph, the Applicant has identified the starting material, MBIE, as a potential impurity. This impurity was quantified using an in-house method and was limited on the specification by the limit of 0.1 % for 'single unknown impurities', which is considered acceptable.

Residual solvents

Residual solvents used in the manufacturing process of meloxicam which are limited on the specification in line with VICH limits are methanol and *o*-xylene.

Batch analysis

Satisfactory batch data has been provided for three full scale batches.

Excipients

Excipients described in a Pharmacopoeia

Microcrystalline cellulose and carboxymethylcellulose sodium (Dispersible cellulose)	BP
Xanthan gum	Ph.Eur.
Sodium benzoate	Ph.Eur.
Sodium saccharin	Ph.Eur.
Glycerol	Ph.Eur.
Sorbitol	Ph.Eur.
Citric acid monohydrate	Ph.Eur.
Sodium hydroxide	Ph.Eur.
Purified water	Ph.Eur.

Excipient(s) not described in a Pharmacopoeia

None.

All excipients comply with their respective monographs and typical certificates of analysis demonstrating compliance for each have been provided.

Packaging

Meloxivet 0.5 mg/ml Oral Suspension for Dogs is presented in bottles of 10 and 30 ml, and Meloxivet 1.5 mg/ml is presented in bottles of 10, 30 and 150 ml, respectively**.** All bottles of both strengths consist of a Type III Amber glass bottle. 10 ml bottles have an HDPE screw cap (closure with LDPE insert), while 30 ml bottles and the 150 ml bottle have a PP screw cap with HPDE liner and separate LDPE insert. There are two syringes, an amber syringe for the 0.5 mg/ml presentation and a clear syringe for the 1.5 mg/ml presentation. Both syringes consist of a polypropylene barrel and plunger with body weight graduation markings printed directly onto the syringe. A number of routine tests were performed such as for the appearance of the glass bottle and syringe, IR spectrum for the screw cap, insert and dosing syringes. Dosing accuracy was performed for the syringes.

The various components were found to be compliant with the relevant Ph. Eur. requirements. Specifications including diagrammatic specifications and certificates of analysis demonstrating compliance with the specifications were provided for all components.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The Applicant has provided a declaration that the excipients and active ingredient are not of animal origin and that no materials of animal origin are used in the process. The DMF holder has provided a declaration of compliance with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01-Rev.2) for the active substance.

CONTROL TESTS ON THE FINISHED PRODUCT

Product Specification and Routine Tests

The finished product release and shelf life specifications were provided and are identical for both product strengths.

Scientific Data

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

The assay method for meloxicam and sodium benzoate and the related substance method were provided and were adequately validated. Appropriate certificates of analysis regarding the working standards of meloxicam and MBIE from the active substance manufacturer and of sodium benzoate from the dosage form manufacturer were used in the validation studies.

Batch analyses

Batch data demonstrating full compliance with the specifications were provided for three batches of each strength.

Stability

Stability Tests on the Active Substance(s)

An ongoing stability programme was described in the DMF with 1 batch added to the programme every year that batches of the raw material are manufactured. Data were presented and were found acceptable.

Stability Tests on the Finished Product

A stability study was initiated on three batches of each product strength. Samples were stored at 25°C/60%RH, 30°C/65% RH and 40°C/75% RH and twelve month data were available at all temperatures. The study at 25°C and 30°C is ongoing to 36 months. All relevant parameters of the specification were tested. All parameters remained within specification.

The data demonstrated a stable profile and extrapolation demonstrated that batches will remain within the 95-105 % limits up to 24 months. Given the satisfactory accelerated results extrapolation was acceptable. The data supported the absence of a storage precaution for the product.

In-use Stability Tests

In-use stability testing was conducted on two freshly manufactured batches of each product strength In-use stability testing at the end of shelf life is planned. Full testing was carried out at 0, 3 and 6 months and additional samples were withdrawn periodically during the course of the 6 months. The presented data supported the proposed in-use period of 6 months.

Forced Degradation Studies

Forced degradation studies were carried out under:

- accelerated conditions of 50°C over 6 months
- Cyclic conditions of -15°C/+30°C and +5°C/40°C over 15 days
- Photostability not less than 1.2 million lux

No significant changes were observed in the accelerated and cyclic conditions studies. No impurities were observed and all relevant parameters remained within specifications for both formulations.

The photostability study justified the packaging of the medicinal product in amber vials to protect it from light, as a significant reduction was observed in active substance and preservative content in both formulations with the appearance of several degradation compounds.

OVERALL CONCLUSION ON QUALITY

Overall the quality of the product was found to be satisfactory.
The Applicant has committed to submit for approval by way of variation, any changes to the process arising from full scale process validation.

3. SAFETY ASSESSMENT

As essential similarity to the reference product was confirmed, the results of toxicological and pharmacological tests and clinical trials were not required in accordance with Article 13 of Directive 2001/82/EC, as amended

Pharmacodynamics

No data are presented in accordance with provisions of Article 13(1) of Council Directive 2001/82/EC (as amended).

Pharmacokinetics

See efficacy part

Toxicology

Toxicological studies

As essential similarity to the reference product was confirmed, the results of toxicological and pharmacological tests and clinical trials were not required in accordance with Article 13 of Directive 2001/82/EC, as amended.

Studies of other effects

Special studies

The Applicant conducted 3 user safety studies with the test product (final formulation); dermal and ocular irritation studies and a dermal sensitization study (local lymph node assay). Based on the findings of the studies reported below, the test product (final formulation) can be considered non-irritating to the rabbit eye and non-irritating to rabbit skin. In addition, it does not demonstrate contact allergic potential (it is a non-sensitizer).

Ocular Irritation Study

This was a GLP study conducted according to OECD test guideline no. 405. A volume of 0.1ml of the test item was applied to the left eye of each of three young New Zealand White rabbits (1 male and 2 females). Scoring for irritation effects was performed at 1, 24, 48 and 72 hours post administration. Based on the findings of this study, the test item was considered 'not irritating' to the rabbit eye.

Dermal Irritation Study

This was a GLP study conducted according to OECD test guideline no. 404. A volume of 0.5ml of the test item was applied by topical semi-occlusive application to the shaved left flank of three young New Zealand White rabbits (1 male and 2 females). The duration of treatment was 4 hours and scoring for irritation effects was performed at 1, 24, 48 and 72 hours post removal of the dressing. Based on the findings of this study, the test item was considered 'non- irritating' to rabbit skin.

Local Lymph Node Assay in mice – Identification of contact allergens

This was a GLP study conducted according to OECD test guideline no. 429. This test was performed in 3 groups of 4 female mice. The test item was applied topically to the dorsum of each ear lobe at concentrations of 25% or 50% (in ethanol/water) or 100% (undiluted) once daily for three days. A control group was treated with vehicle (ethanol/water only). On the third day slight erythema of the ear was observed in the mice treated with the test item at concentrations of 50% and 100%. Five days after the first topical administration of the test item each mouse was injected intravenously with radiolabelled thymidine. All mice were sacrificed 5 hours after injection and the draining auricular lymph nodes were excised and pooled per group. Based on the findings of this study, the test item was classed as a non-sensitizer.

User safety

Inherent Toxicity

Given that Meloxivet is demonstrated to be bioequivalent to Metacam, the potential impact of the active substance in respect of user safety will be the same for both products. In addition, the excipients used in the formulation are well established and have an extensive history of use in oral preparations at concentrations comparable to those specified for Meloxivet. Given the known use of the excipients and the expected safety profile, it is not expected that the excipients will present a hazard to the user.

Exposure of the user

The Applicant notes that the intended posology and indications are identical to those of the reference product, therefore, the same exposure scenarios exist.

Conclusion including the risk management proposals

Risk management phrases as authorised for Metacam are included in the SPC and product literature:

- People with known hypersensitivity to NSAIDs should avoid contact with the veterinary medicinal product.
- In case of accidental self administration, seek medical advice immediately and show the package insert or the label to the physician.

Based on the fact that bioequivalence is demonstrated with Metacam Oral Suspension, that the excipients included in the formulations can be considered safe and that the posology and indications are identical to those of the reference product, it can be accepted that the potential risk to the user posed by Meloxivet Oral Suspension will not be any greater than that posed by the reference product.

Environmental safety

Phase I Assessment

The Applicant refers to the Guideline on Environmental Impact Assessment for Veterinary Medicinal Products – Phase 1 (CVMP/VICH/592/98-FINAL).
Given that the product is:

- for non-food animals,
- for individual treatment under veterinary prescription, and
- extensively metabolised prior to excretion mainly in the faeces which, in the dog, is of minimal environmental relevance,

the environmental risk assessment stops at Phase I.

OVERALL CONCLUSIONS ON SAFETY

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 show that the test product (Meloxivet 1.5 mg/ml Oral Suspension for Dogs) is bioequivalent to the reference product (Metacam 1.5 mg/ml Oral Suspension for Dogs); consequently, it can be concluded that the systemic effects of the two products in respect of safety will be the same. In addition, the Applicant has provided *in vitro* dissolution data confirming that the conclusions of the *in vivo* study can be reliably extrapolated to the 0.5 mg/ml formulation. The product when used in accordance with label recommendations is not expected to represent a risk to the user or to the environment.

4. EFFICACY ASSESSMENT

The proposed indication for Meloxivet 0.5 mg/ml Oral Suspension for Dogs and Meloxivet 1.5 mg/ml Oral Suspension for Dogs is for the alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders in dogs**.** The recommended posology consists of an initial single dose of 0.2 mg meloxicam/kg body weight on the first day, followed by once daily administration (24-hour intervals) of 0.1 mg meloxicam/kg body weight. The product is to be administered mixed with food, and measured using a measuring syringe as supplied with the product.

As essential similarity to the reference product was confirmed, the results of toxicological and pharmacological tests and clinical trials were not required in accordance with Article 13(1) of Directive 2001/82/EC, as amended.

Pharmacokinetics

A pivotal GLP pharmacokinetic study with the final test product formulation was conducted for the purpose of concluding on bioequivalence of the test item (Meloxivet 1.5 mg/ml oral suspension) and the reference item (Metacam 1.5 mg/ml oral suspension). The study was designed to meet the requirements of the Guideline for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMEA/CVMP/016/00).

Pivotal Bioequivalence Study in Dogs

Study status
This was a GLP compliant two-period, two-treatment, two-sequence crossover study. The study was randomised and blinded.

Objective
To determine whether a new generic oral formulation of meloxicam (Meloxivet oral suspension) was bioequivalent to the authorised reference formulation of meloxicam (Metacam oral suspension) in dogs.

Test article
Meloxivet (1.5 mg meloxicam /ml) oral suspension: this was the proposed commercial formulation. A certificate of analysis was provided.

Reference article
Metacam (1.5 mg meloxicam /ml) oral suspension; this was an existing commercial formulation.

Animals
24 healthy male Beagle dogs; aged 9.0 - 12.5 months, weight 9.6 - 15.8kg at the start of treatment. Randomised according to bodyweight into 2 treatment sequences of 12 dogs each.

Treatments
Each treatment period consisted of five consecutive treatment days: a loading dose of 0.2mg meloxicam/kg on the first day of treatment, followed by a daily maintenance dose of 0.1mg meloxicam/kg for the following 4 days. The test item or reference item was administered by oral gavage, after the animals had been fed.

Observations
During the study, all animals were examined daily to evaluate their general health status.

Samples
Blood samples for the determination of meloxicam concentration in plasma were collected before treatment (0 min), at 30 min and at 1, 2, 3, 6, 9, 12, 16, 24, 48, 72, 96, 96.5, 97, 98, 99, 102, 105, 108, 112, 120, 144, 168, 192 and 216 hours after the first administration in each treatment period. All plasma samples were stored at approximately – 20Cº ($\pm$ 5ºC) until they were analysed.

Assay
Meloxicam in plasma was quantified using reverse phase HPLC with UV detection.
Quantification of the samples was by measurement of the sample peak responses in comparison to a standard line prepared from spiked plasma of known concentration in the range 25-2500 ng meloxicam /ml plasma. QC samples (25, 500 and 2000 ng/ml) were included with each analytical run. The performance of the assay, based on the results of the QC samples, was acceptable.

Evaluation
Pharmacokinetic parameters were calculated using WinNonlin v4.1 pharmacokinetic software with a non-compartmental approach. The following pivotal parameters were determined:
- C_{max}, after the fifth (last) dosing of each treatment period.
- $AUC_{(96h-120h)}$ after the fifth (last) dosing of each treatment period.

A number of supporting parameters were also determined. These included:
- C_{max} after the first dosing of each treatment period
- T_{max} after the first and fifth dosing of each treatment period
- $T_{1/2}$ after the fifth dosing of each treatment period
- $AUC_{(0h-24h)}$ obtained after the first dosing of each treatment period.
- $AUC_{(0h-\infty)}$ obtained after the fifth dosing of each treatment period.
- C_{ss} (=$AUC_{(96h-120h)}$/24) – average steady-state concentration for both treatment periods.

Statistics
After natural logarithmic transformation, $AUC_{(96h - 120h)}$ and C_{max} were analysed by ANOVA. The ANOVA-model with the treatment sequence, treatment period, animal (nested in the treatment sequence) and treatment factors was performed.

For both parameters, 90% confidence intervals for the ratios of the two treatment means (test/reference) were calculated. In the study protocol, the criteria for accepting bioequivalence were defined as 90% CI for $AUC_{(96h - 120h)}$ and C_{max} falling within the limits 80% to 125% and 70% to 143%, respectively.

Results
Individual plasma concentrations and curves were presented.

The plasma concentration profiles for both reference product and test product were very similar throughout the period of sampling. On Day 1 of treatment (administered dose 0.2 mg meloxicam/kg), both profiles were characterised by a rapid increase to peak concentrations of 631.34 and 578.09 ng/ml at 4.75 to 4.33 hours, respectively for the reference and the test product. On Day 5 of treatment (administered dose 0.1 mg meloxicam/kg), peak concentrations of 623.09 and 659.59 ng/ml were achieved for the reference and the test product, respectively.

The following arithmetic mean (±SD) parameters were obtained for day 5 of treatment.

Treatment	**C_{max} (ng/ml)**	**T_{max} (h)**	**$AUC_{(96h - 120h)}$ (ng.h/ml)**	**T½ (h)**	**Css**
Meloxivet	659.59 (172.70)	6.08 (6.14)	12091.70 (3685.83)	24.46 (5.80)	503.82 (153.58)
Metacam	623.09 (170.02)	6.71 (6.79)	11558.35 (3711.08)	24.04 (5.90)	481.60 (154.63)

Parameter	**90% Confidence Intervals of the ratio**	**Point estimate (Meloxivet relative to Metacam)**
$AUC_{(96h - 120h)}$	98.18 – 114.54	106
C_{max}	96.17 – 118.14	107

Conclusion
The ratios of the two treatment means for $AUC_{(96h - 120h)}$ and C_{max} fell within the limits of 80-125%, which, in accordance with the bioequivalence guideline (EMEA/CVMP/016/00), can be considered demonstrative of bioequivalence.

The number of animals used was based on the findings of previous studies: it was established that a sample size level of 24 animals would be sufficient to determine bioequivalence with a power of 90% and a 5% significance level. The Applicant stated that there is no known statistically significant effect of gender on pharmacokinetics and therefore, the use of male dogs only is acceptable. Sampling times extended to at least 3 elimination half-lives beyond the time taken to reach maximum concentration.

The test and reference items were administered by oral gavage and 10ml of water was flushed along the tube after administration. The use of gavage was justified on the basis that it facilitates standardising the timing of treatment. This was a multi-dose study and both test item and reference item were administered at the rates intended for normal use. The Applicant stated that efficacy of meloxicam depends on steady state conditions. Consequently, use of a multidose study as required by the Guideline was considered to be appropriate. The duration of therapy (5 days) was justified on the basis that steady-state is reached after 3 to 5 days therapy.

The CVMP accepted that the use of a multidose study is appropriate, given that when repeated treatments are administered, there is the potential for meloxicam accumulation with a treatment interval of 24 hours and steady-state conditions are reached after 3-5 days treatment. Based on the data provided, the test item (Meloxivet 1.5 mg/ml) and the reference item (Metacam 1.5 mg/ml) were considered bioequivalent.

The Applicant has also provided comparative *in vitro* dissolution data between Meloxivet 0.5mg/ml oral suspension and Meloxivet 1.5 mg/ml oral solution. These data confirmed that release of the active substance from the suspension will occur at a similar rate for both presentations. Consequently, it was accepted that data for the Meloxivet 1.5 mg/ml presentation can be extrapolated to the Meloxivet 0.5 mg/ml presentation.

Validation of the analytical method for the determination of meloxicam in canine plasma

The analytical method was validated in a GLP study. Some additional validation was conducted as part of the bioequivalence study.

Linearity was over a concentration range including the LOQ and seven other points
(range, 25 - 2500 ng/ml). The accuracy, the recovery and the precision were evaluated by analysing the QC samples (three concentrations, 25 (LOQ), 500 and 2000 ng/ml).

- In support of the specificity of the method, the analysis of non-spiked samples showed the absence of interfering peaks.
- Linearity was confirmed over the range 25-2500 ng/ml (r = 0.999).
- Values for accuracy and precision were within pre-defined limits.
- Absolute recovery ranged from 88 to 97%.
- The lower LOQ was 25 ng /ml and the LOD was calculated to be 4.3 ng/ml.
- Stability of meloxicam under the following test conditions was confirmed: in processed samples stored for 5 days at 4°C; in dog plasma for 4 months at -25°C ($\pm$ 5°C); and, through 3 freeze thaw cycles.

Based on the validation data presented, the method is sufficiently accurate and precise for the determination of meloxicam in canine plasma.

The safety profile of Meloxivet is comparable to Metacam and therefore the same warnings are included in the SPC and product literature, as follows:

- Do not use in pregnant or lactating animals
- The safety of the veterinary medicinal product has not been established during pregnancy and lactation
- Do not use in animals suffering from gastrointestinal disorders such as irritation and haemorrhage, impaired hepatic, cardiac or renal function and haemorrhagic disorders, or where there is evidence of individual hypersensitivity to the product.
- Do not use in dogs less than 6 weeks of age
- Typical adverse drug reactions of NSAIDs such as loss of appetite, vomiting, diarrhoea, faecal occult blood and apathy have occasionally been reported. These side effects occur generally within the first treatment week and are in most cases transient and disappear following termination of the treatment but in very rare cases may be serious or fatal.
- If side effects occur, treatment should be discontinued and the advice of a veterinarian should be sought.
- Avoid use in any dehydrated, hypovolaemic or hypotensive animal, as there is a potential risk of increased renal toxicity.
- Other NSAIDs, diuretics, anticoagulants, aminoglycoside antibiotics and substances with high protein binding may compete for binding and thus lead to toxic effects. Meloxivet must not be administered in conjunction with other NSAIDs or glucocorticosteroids.

- Pre-treatment with anti-inflammatory substances may result in additional or increased adverse effects and accordingly a treatment free period with such drugs should be observed for at least 24 hours before the commencement of treatment. The treatment-free period, however, should take into account the pharmacokinetic properties of the products used previously.

The information relating to adverse effects, precautions for use, interactions and overdose included on the proposed SPC for Meloxivet is similar to that included on the SPC of the reference product, Metacam. It is noted that for both presentations, the volume of product for administration to clinical cases will be determined by means of a graduated syringe. The concentration of the product will be printed on the syringe and the colours of syringes will be different for each concentration.

5. BENEFIT RISK ASSESSMENT

The application for Meloxivet 1.5 mg/ml oral suspension and Meloxivet 0.5mg/ml oral suspension is a generic application. The aim of the development work was to develop an oral suspension essentially similar to the reference product Metacam (containing meloxicam) 1.5 mg/ml oral suspension for dogs. The composition is based on the composition of the reference product. The active substance meloxicam is manufactured by one manufacturer who has submitted a complete DMF. Overall, the quality of the product was found to be satisfactory.

As essential similarity to the reference product was confirmed, the results of toxicological and pharmacological tests and clinical trials were not required in accordance with Article 13(1) of Directive 2001/82/EC, as amended.

A pivotal bioequivalence study was performed in 24 adult male beagle dogs. The study was a a GLP compliant, two-period, two-treatment, two sequence crossover study, comparing the new generic formulation of meloxicam (Meloxivet oral suspension 1.5 mg/ml) versus the reference Metacam oral suspension 1.5 mg/ml. The plasma concentration profiles for both reference and test product were very similar throughout the period of sampling. The ratios of the two treatment means for $AUC_{(96h - 120h)}$ and C_{max} fell within the limits of 80-125%, which, in accordance with EMEA/CVMP/016/00, can be considered demonstrative of bioequivalence.

Further, comparative *in vitro* dissolution data between Meloxivet 0.5mg/ml oral suspension and Meloxivet 1.5 mg/ml oral solution were presented. From the dissolution profiles generated, it was evident that in both dissolution media the two strengths of Meloxicam oral suspension, as well as the two batches of each strength, showed similar dissolution behaviour. These data confirm that release of the active substance from the suspension will occur at a similar rate for both presentations. Consequently, it is accepted that data for the Meloxivet 1.5 mg/ml presentation can be extrapolated to the Meloxivet 0.5 mg/ml presentation.

The safety of Meloxivet to the target species and to the user has been established by:

- the bioequivalence between the two products;
- a satisfactory impurity profile of meloxicam in Meloxivet;
- the fact that a comparable safety profile was obtained with both products in the bioequivalence study.
- the excipients used in the formulation are well established and have an extensive history of use in oral preparations at concentrations comparable to those specified for Meloxivet. Given the known use of the excipients and the expected safety profile, it is not expected that the excipients will present a hazard to either the target animal or the user.
- a declaration has provided by the Applicant that the excipients and active ingredient are not of animal origin and that no materials of animal origin are used in the process.

Target animal and user safety warnings are the same as those for the reference product. No impact on the environment is anticipated.

Risk management statements as authorised for Metacam are included in the SPC and product literature:

- People with known hypersensitivity to NSAIDs should avoid contact with the veterinary medicinal product
- In case of accidental ingestion, seek medical advice immediately and show the package insert or the label to the physician.

Meloxivet will be used in the same way as Metacam, and thus the exposure of the user will be the same for both products and the same warnings are appropriate.

Efficacy has been established by demonstration of essential similarity to the reference product, Metacam, by confirmation of bioequivalence between the two products when administered as recommended to the target species, dogs.

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