SCIENTIFIC DISCUSSION

1. SUMMARY OF THE DOSSIER

The application concerns Flexicam, a generic medicinal product as defined in Article 13 of Directive 2001/82/EC as amended. 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 (NSAID) 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 oral suspension is to be administered mixed with food, and measured using a drop dispenser or measuring syringe as supplied with the product. The amount of suspension to be used is measured either as drops (for small dogs) or using a special dosing syringe (for larger dogs), and poured on the food.

In October 2008, CVMP agreed to authorise an extension application to Flexicam. The intended new pharmaceutical form, solution for injection 5mg/ml for dogs and cats, has been formulated to be pharmaceutically equivalent to the reference product Metacam 5mg/ml solution for injection for dogs and cats. The solution for injection is to be administered subcutaneously or intravenously.

For Flexicam solution for injection, the recommended posology for treatment of musculo-skeletal disorders in dogs is a single subcutaneous injection at a dosage of 0.2 mg meloxicam/kg bodyweight with continuation of treatment using the oral suspension, or for the reduction of post-operative pain (over a period of 24 hours) a single intravenous or subcutaneous injection of 0.2 mg meloxicam/kg body weight before surgery. In cats the posology for the reduction of post-operative pain is a single subcutaneous injection of 0.3 mg meloxicam/kg body weight before surgery.

2. QUALITY ASSESSMENT

Composition of Oral suspension 1.5mg/ml for dogs

Qualitative Composition	Quantitative composition (mg/ml)	Function	Reference to analytical quality
Active Substance			
Meloxicam	1.5	Active substance	BP
Other ingredients			
Dispersible cellulose			Ph. Eur.
Xanthan gum			
Sodium benzoate	1.5		
Glycerol			
Xylitol			
Sodium lauryl sulphate			
Citric acid monohydrate			
Sodium citrate			
Honey flavour			
Simethicone emulsion			
Purified water			

Composition Solution for injection 5mg/ml for dogs and cats

Qualitative Composition	Quantitative composition (mg/ml)	Function	Reference to analytical quality
Active Substance Meloxicam	5.0	Active substance	BP
Other ingredients Ethanol anhydrous* Poloxamer 188 Glycofurol Meglumine Glycine Sodium chloride Sodium hydroxide Water for injections	150.0		Ph. Eur.

Container of Oral suspension for dogs

Container Sizes	Description	Composition	Dosing device	Closure
10 ml 32 ml 100 ml	White opaque bottle	HDPE/LDPE	White opaque LDPE dropper nozzle and PP oral dosing syringe	White opaque screw-on HDPE/PP cap

Container of Solution for injection for dogs and cats

Container Sizes	Description	Composition	Closure
10 ml	Clear Ph. Eur. Type 1 glass vial	Glass	20 mm grey Ethylene Propylene Diene Monomer (EPDM) rubber stopper with a 20 mm Aluminium flip-off violet coloured seal

Regarding the oral suspension, the bottles used have a dropper nozzle in the neck which is designed for administration of the lowest dose range for small dogs. Larger dogs are catered for by the use of an oral dosing syringe which is supplied with each pack.

Clinical Trial Formula

The formula used in the bioequivalence study for the oral suspension was identical to that detailed above. A certificate of analysis for the batch used was presented.

Flexicam and Metacam solutions for injection were accepted to be bioequivalent as they have the:

- Same qualitative and quantitative composition
- Same profile of impurities and degradation products of active substance
- Same pharmaceutical form

Development Pharmaceutics

The product has been formulated as a generic of the reference product Metacam oral suspension. The product contains Meloxicam at a concentration of 1.5 mg/ml and is presented as an oral suspension. Bioequivalence is discussed in Part III. Preservative efficacy in line with Ph. Eur. 5.1.3. for oral products has been demonstrated. In order to help establish essential similarity, batch data, including the impurity profile of Flexicam and Metacam were compared. Data were presented for two batches of each product, packaged in 10 ml and 100 ml vials.

The Applicant has demonstrated that the differences in pH between the product and the reference product are not significant with respect to dissolution or bioequivalence as the difference is small and the active is insoluble in the pH range in question. The Applicant has effectively demonstrated that the particle size profile of the finished product reflects the particle size of the excipient, dispersible cellulose, rather than that of the active substance. Furthermore, the Applicant has demonstrated that the manufacturing process does not affect the particle size of the active substance by testing particle size of the slurry (manufactured without cellulose) before and after milling. The impurity profile of the two products was shown to be comparable.

There is no requirement for the excipients of the formulation to be identical to that of the reference product. The excipients used in this formulation are widely used in pharmaceutical products and the role of each in the formulation was described.

The packing material was also chosen with reference to that of the reference product. No specific compatibility studies have been carried out but the stability data presented are considered to adequately address this issue. The product utilises two dosing devices, a syringe and an integrated dropper. Uniformity of delivered dose from both has been investigated.

Flexicam solution for injection has been formulated to be pharmaceutically equivalent to the reference product, Metacam 5 mg/ml solution for injection for dogs and cats.

METHOD OF PREPARATION

Manufacturing Formula and Batch Size

Oral Suspension
The manufacturing formulation for a 500 litre batch size was presented.

Solution for injection
The manufacturing formula for a 50 litre batch size was presented.

Manufacturing Process and In-process Controls

Oral suspension
Manufacture involves the preparation and combination of a number of solutions/suspensions, homogenisation and milling. At some steps in the process, mixing is continued 'until dissolved' or 'to form a homogeneous slurry'. Temperature and pH are monitored before and after colloid milling. Samples are taken from the top and bottom of the bulk tank prior to filling and submitted for analysis. Fill volumes are checked every 2 hours and a sample bottle subjected to a vacuum test twice per shift.

Solution for injection
Manufacturing involves the sequential addition of each of the ingredients to form a 'bulk solution'. The pH of the bulk solution is adjusted, final mixing takes place and the bulk solution is subjected to sterile filtration followed by vial filling and terminal sterilisation of the filled vials. A flow chart of the manufacturing process was presented.

Validation of the Manufacturing Process

Oral suspension

Process validation data were provided. Meloxicam, preservative content and pH were tested. All results are within specification. In-process controls for the process validation consist of parameters that are monitored during manufacture.

Two different batches of meloxicam raw material were used in the manufacture of the process validation batches. Comparison of the impurity profile of the process validation batches demonstrates that the manufacturing process does not lead to degradation of the active substance.

Solution for injection

Process validation has been carried out for three 50 litre (production scale) batches of the product. The process validation protocol identifies parameters within the various stages of the manufacturing process which require monitoring during process validation (i.e. those which may have an impact on product quality) by way of determining the reproducibility of the manufacturing operation. Validation of the manufacturing process is principally concerned with establishing / confirming processing times for addition of ingredients during preparation of the bulk solution and is also concerned with confirming the integrity of the sterile filter. Samples of filtered bulk solution were tested for pH and assay of the active substance and preservative.

CONTROL OF STARTING MATERIALS

Active Substance
Specification and routine tests
Active ingredients listed in a Pharmacopoeia.
An Active Substance Master File (ASMF) for meloxicam was provided. This supercedes the previous ASMF dated July 2004 which was provided in the Flexicam procedure and includes a summary document which clearly outlines the changes that appear in the March 2007 version. Minor updates to the ASMF have been made and do not impact on the route of synthesis or quality of the raw material. No questions arise as a result of these updates. The ASMF specification was in line with the BP monograph for the raw material. Additional limits were also detailed within the methodology section. Residual solvents limits are within VICH requirements.

Analytical methods and validation
Assay of meloxicam is by non aqueous titration and related substances are determined by HPLC. Both methods are as described in the BP monograph. Other relevant test methods described are those of the BP monograph. Additional in-house methods were also described. A GC method for determination of the residual solvents methanol, isopropyl alcohol, ethyl acetate and o-xylene and a separate GC method for determination of dimethylformamide are described. The methods have been validated.

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. Particle size data for three production scale batches were presented in the ASMF. Certificates of analysis, including polymorphic form were provided for three batches.

Physico-Chemical Characteristics liable to affect bioavailability
Certificates of analysis, including polymorphic form, were provided for the batches presented. The working standard has been characterised according to the monograph in the British Pharmacopoeia with regards to identification, related substances, loss on drying and assay.

Scientific data - Nomenclature

International Non-proprietary Name (INN)	Meloxicam
IUPAC Name	4-hydroxy-2-methyl-N-(5-methyl-1,3-thiazol-2-yl)-2H-1,2-benzothiazine-3-carboxamide-1-1-diaoxide
National Approved Names:	USAN: Meloxicam BAN: Meloxicam JAN: Meloxicam
CAS Number	[71125-38-7]
Synonyms and Abbreviations	None
Molecular Formula	$C_{14}H_{13}N_3O_4S_2$
Molecular Weight	351.41

Manufacturing description
Isopropyl-4-hydroxy-2-methyl-2-benzothiazine-3-carbosylate-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 and ^{1}HNMR. 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 British Pharmacopoeia monograph. No literature describes isomerism for meloxicam. The working standard is obtained from a commercial batch and has been characterised. The meloxicam impurity standard is used routinely when analysing meloxicam for impurities. The working standard has been characterised according to the monograph in the British Pharmacopoeia with regards to identification, related substances, loss on drying and assay.

Impurities
As well as the impurities listed in the BP monograph, the Applicant has identified the starting material, Methyl benzothiazine isopropyl ester, as a potential impurity. Forced degradation studies have established that meloxicam in the solid state is stable with respect to exposure to UV light and ambient and accelerated storage temperatures. On exposure to elevated temperature (220°C for 48 hrs) significant degradation occurs (approx 1.0 %). In the liquid state meloxicam exhibits some degradation on exposure to acid and base hydrolysis and oxidation and is stable with respect to reduction and UV exposure. The degradation products do not co-elute with the meloxicam peak and the assay is therefore considered to be stability indicating.

Residual solvents
Five solvents are used in the manufacture of meloxicam and are therefore potentially present in the raw material. All five are routinely limited on the specification. The limits and levels of each found in three commercial scale batches were presented.

Solvents used in the manufacture of the starting material 2-amino-5- methylthiazole are methanol, methylene dichloride and toluene. Methanol is already limited on the meloxicam specification and the other two solvents are class 2 solvents with VICH limits of 600 ppm and 890 ppm respectively. Methylene dichloride and toluene have been shown to be undetectable in 10 batches of meloxicam and the absence of limit for these solvents in the specification is considered justified. (LOD for toluene is 4 ppm and for methylene chloride is 20 ppm).

The ASMF also contains a satisfactory justification why the potential contaminants of toluene and methylene dichloride, benzene and 1,2-dichloroethane do not require to be routinely tested.

Batch analysis
Satisfactory batch data has been provided for three full scale batches for the two pharmaceutical forms. The certificates of analysis detail all tests listed on the specification including the in-house tests which are additional to the BP specification.

Excipients
Specifications and routine tests
Excipients described in a Pharmacopoeia for Flexicam Oral suspension

Dispersible cellulose	Ph. Eur.
Xanthan gum	
Sodium benzoate	
Glycerol	
Xylitol	
Sodium lauryl sulphate	
Citric acid monohydrate	
Sodium citrate	
Simethicone emulsion	
Purified water	

Specifications and routine tests
Excipients described in a Pharmacopoeia for Flexicam Solution for injection

Ethanol Anhydrous	Ph. Eur.
Poloxamer 188	
Meglumine	
Glycine	
Sodium Chloride	
Sodium Hydroxide	
Water for injection	

Excipient not described in a Pharmacopoeia

Oral suspension

Honey flavour:	The honey flavour is a blend of artificial, nature identical and natural flavouring substances. It is regarded as having GRAS status as the ingredients are approved under FDA regulations.

Scientific data
Specifications and typical suppliers' certificates of analysis are provided for all the pharmacopoeial excipients demonstrating compliance with their respective monographs. The Applicant has confirmed that the excipients comply with the VICH residual solvents guideline.

Solution for injection

Glycolfurol.: The specification for glycofurol is adequate and includes specifications for description, solubility, pH, refractive index, density, water, colour, peroxides, chlorides, sulphates, heavy metals, related substances, molecular weight and composition.

Scientific data
Specifications and methods of analysis of all of the pharmacopoeial grade excipients are provided and demonstrate compliance with their respective monographs.

Packaging Material (Immediate Packaging)

Oral suspension
The product is presented in three bottle sizes: 10, 32 and 100 ml. The bottles are composed of a blend of white opaque HDPE and LDPE. The inner component of the cap is composed of white opaque HDPE and the outer component is white opaque PP. The nozzle is composed of white opaque LDPE. The oral dosing syringe provided is composed of a transparent polypropylene barrel and a white opaque polypropylene plunger.

Diagrammatic and dimensional specifications of the containers were provided. Compliance for the various components with the European Pharmacopoeia was shown.

Solution for injection
The product is presented in one vial size of 10 ml. The 10 ml vials are composed of clear Ph. Eur. Type 1 glass. The 20 mm rubber stoppers are composed of grey EPDM and there is a 20 mm aluminium flip-off violet seal.

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

An annex III declaration was provided for the product by the Applicant as well as individual declarations from the suppliers of the active substance and excipients. The product does not contain any materials of animal origin.

CONTROL TESTS ON THE INTERMEDIATE PRODUCT

The only intermediate identified in the production of the product is the bulk solution prior to filling of the vials (i.e. the post filtration solution). The specification applied to the intermediate product includes tests for description, pH, assay (of active substance and of preservative) and weight of solution per ml.

CONTROL TESTS ON THE FINISHED PRODUCT

Product Specification and Routine Tests:

Scientific Data
Analytical validation of methods and comments on the choice of routine tests and standards
The analytical tests for identification and assay of Meloxicam are based on those described in the BP Vet monograph for Meloxicam oral suspension. The method was adequately validated. An analytical method for determination of the preservative was developed by the manufacturer. The method has

been adequately validated. The method for determination of related substances is based on that described in the BP monograph for the raw material. The method has also been adequately validated.

The analytical tests for identification and assay of Meloxicam are based on those described in the BP Vet monograph for Meloxicam oral suspension. The method was adequately validated. An analytical method for determination of the preservative was developed by the manufacturer. The method has been adequately validated. The method for determination of related substances is based on that described in the BP monograph for the raw material. The method has also been adequately validated.

Batch analyses

The Applicant agreed to provide compliant batch data when the release specification is finally agreed. A timeframe for provision of the data (after agreement of the specification) has been provided. The Applicant has confirmed that the product will be retested to the complete finished product specification on its entry to the EU.

Stability

Stability Tests on the Active Substance

The long-term stability study at 25°C/60% RH is scheduled to continue for 66 months and 1 batch per year will be added to the stability program. A re-test period of 24 months with no specific storage precautions was accepted.

Stability Tests on the Finished Product

Oral suspension

Results were presented for batches packaged into all three pack sizes up to the 6 month time-point. Real time studies are to extend to 36 months.

Under accelerated conditions there is similar variability in active substance content with no obvious trend of decrease.

Stability data including real-time testing at 9 and 12 months for the three stability batches were provided.

In the SPC, the Applicant proposed a 2 year shelf life and a 9 month in-use shelf life, with no specific storage conditions, and this was found to be acceptable. A stability study in freeze-thaw cycling has also been conducted.

Solution for injection

Results for 6 and 12 months are presented for all three batches stored under long-term and accelerated conditions.

Photostability

No significant change was observed in any of the batches in any containers exposed to light for up to 15 hours.

In-use Stability Tests

Oral suspension

Results are presented for two batches packaged into 10 ml and 100 ml vials up to the 3 month time-point. No significant change was observed in any of the batches. No results are available for preservative efficacy as this was not scheduled for the 3 month analysis time point but satisfactory preservation has been demonstrated for a batch manufactured to contain the lower shelf life limit of 1.35 mg/ml. The Applicant has provided a commitment to repeat the in-use stability study with product approaching the end of the shelf life.

Solution for injection
All three batches used for stability studies were also subjected to in-use stability testing. Results presented for the three batches indicate that none of the parameters tested change significantly during the 28 day test period. These data support the proposed 28 day in-use shelf-life for the product.

In-use stability data was also presented in Part II.A for development batch OMMEP1015-A which had been stored at 40°C/75%RH for 6 months after product release. A commitment to carry out in-use testing on product at the end of its shelf-life was provided.

OVERALL CONCLUSION ON QUALITY

Oral suspension
The quality of the finished product at release and throughout shelf-life was considered to be demonstrated with the addition of a number of commitments which relate to process validation, residual solvent declaration, honey flavour, specification and stability and are to be addressed in writing.

Solution for injection
Overall, the quality of the product was found to be satisfactory. Commitments have been made relating to the specification of a residual solvent, an analytical certificate for meglumine and a diagrammatic representation of one of the packaging components.

3. SAFETY ASSESSMENT

As generic status 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.

A combined Safety and Efficacy Expert report was presented.

Details of the product
Flexicam oral suspension is a pale green uniform suspension.
Flexicam solution for injection is a clear yellow solution.

Pharmacological Studies

Pharmacodynamics
No data are presented, in accordance with the provisions of Directive 2001/82/EC as amended.

Pharmacokinetics
Oral suspension - Demonstration of bioequivalence
The data presented related to a GLP study intended to demonstrate bioequivalence of Flexicam with the authorised reference product Metacam in a study designed to meet the requirements of the Guideline for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMEA/CVMP/016/00) and the Guideline on Statistical principles for Veterinary Clinical Trials (EMEA/CVMP/816/00). See overview of the study below.

Solution for injection - Demonstration of bioequivalence
Exemptions from the need for bioequivalence studies was claimed in accordance with the 'Guideline for the conduct of Bioequivalence studies for Veterinary Medicinal Products' (EMEA/CVMP/016/00-FINAL), point '4b'. This states that:
'Bioequivalence studies are generally not necessary if the product fulfils one or more of the following conditions:

……

b) the product is to be parenterally or orally administered as a solution and contains the same active substance(s) and excipients in the same concentrations as the veterinary medicinal

product currently approved for use in the target species which is the subject of the new application'.
……

Adequate assurance of similarity of composition was provided. Based on the data provided, it was accepted that the claimed exemption applies.

Bioequivalence study in dogs (Oral Suspension)

Study status

This was a classic 2-period, crossover design study, certified as being GLP compliant in accordance with OECD principles.

Objective

To demonstrate the bioequivalence of a new generic formulation of meloxicam (Flexicam) to that of an authorised reference formulation of meloxicam (Metacam) in dogs.

Test articles

i) Flexicam (1.5 mg meloxicam /ml) oral suspension; this was the proposed commercial formulation; a certificate of analysis was provided.
ii) Metacam (1.5 mg meloxicam /ml) oral suspension; this was the existing commercial formulation as authorised by the centralised procedure.

Animals

14 healthy male Beagles, age 4-5 months, weight 7-10 kg, randomly assigned to 2 groups of 7.

Treatments

Dogs received a single dose of 0.2 mg meloxicam / kg bodyweight (highest recommended dose) directly into the mouth using a dosing syringe, approximately 30 minutes after a normal meal. The washout period was more than 10 times the terminal t½ of meloxicam for dogs as published (mean 23.7 hrs).

Observations

Dogs were observed several times daily for appearance and behaviour.

Samples

Blood samples were collected before treatment and at 30 minutes, 1, 3, 6, 8, 10, 24, 48, 72, 120 hours after treatment. Sampling times extended to at least 3 terminal t½ s beyond expected T_{max}. Plasma was stored at approx -20ºC prior to analysis.

Assay

Meloxicam and the internal standard (piroxicam) were extracted from plasma using liquid/liquid extraction then analysed by reverse-phase HPLC with UV detection.

Single test samples were extracted and analysed in batches, with calibration standards prepared in the range 15-5000 ng meloxicam /ml plasma. Duplicates of lowest and highest calibration standards were extracted as a precaution; use of the 2nd duplicate was fully documented if used. Triplicate QC samples were also prepared over the range 30 – 4000 ng/ml, together with blank dog plasma test samples to verify specificity. All standards and QC samples were within acceptable levels.

Test samples with concentration above the analytical range were reassayed following dilution with control plasma. Test samples with concentration below the analytical range were reported as not quantifiable. Example chromatograms were provided.

Validation

The analytical method was validated in a GLP study.

The method was validated over the range 15 – 5000 ng/ml, with acceptable linearity (±15%). No significant interfering substances were found at the retention time of meloxicam or the internal

standard (piroxicam) in dog plasma from 6 sources; therefore specificity was satisfactory. The mean intra- and inter-occasion accuracy (±15%), and precision (CV≤ 15%) were also found to be satisfactory (Overall mean recovery of meloxicam (88.9%) and internal standard (from dog plasma was determined by analysing QC samples in triplicate. The effect of dilution of plasma up to 2.5x was also assessed and considered acceptable.

Meloxicam was stable in dog plasma for at least 4 weeks at -20ºC (this covers the period between sampling and assay). Stability through 3 freeze thaw cycles was also established. Lower LOQ = 15 ng /ml.

Evaluation
Pharmacokinetic parameters were estimated using a non-compartmental approach.
The following parameters were estimated from the plasma concentrations:
- $C_{max(obs)}$, $T_{max(obs)}$ based on observed maximum concentrations
- $AUC_{(0-t)}$ where t = last timepoint where concentrations were considered to be detectable

The following were determined from the slope of the terminal elimination phase:
- $AUC_{(0-\infty)}$, K_{el} (terminal elimination rate constant), $T½_{el}$ and CL/F (clearance)

Statistics
The number of animals used was based on a calculation using published values for C_{max} and AUC for oral meloxicam in dogs (0.464 mg/L and 22.9 mg.hr/L respectively)

After natural logarithmic transformation $AUC_{(0-\infty)}$ and $C_{max(obs)}$ were analysed by ANOVA and compared by point estimates and 90% confidence intervals (acceptance range 0.8 – 1.25).

Point estimates and 90% confidence intervals for $T_{max(obs)}$ were calculated in a similar way but without log transformation (no acceptance limits given)

A sequence effect was not included in the analysis as no predose samples contained detectable concentrations of meloxicam.

Results
Individual plasma concentrations and individual pharmacokinetics were presented.

The following arithmetic mean* pharmacokinetic parameters were obtained (SD in brackets*):

Treatment	**$C_{max(obs)}$ Ng/ml**	**$T_{max(obs)}$* h**	**$AUC_{(0-t)}$ ng.h/ml**	**$AUC_{(0-\infty)}$ ng.h/ml**	**$T½_{el}$ h**	**K_{el} l/h**	**CL/F ml/h/kg**
Flexicam	362 (60.0)	6.0 (3-24)	14471 (3356)	14675 (3354)	18.72 (3.48)	0.03837 (0.008246)	14.53 (4.572)
Metacam	378 (56.5)	6.0 (1-10)	14811 (3087)	15046 (3119)	19.44 (2.25)	0.03608 (0.003930)	13.79 (2.617)

* Tmax values shown as: i) median, not mean; ii)min & max range, not SD

Geometric means for $AUC_{(0-\infty)}$ and $C_{max(obs)}$ were also given in the Pharmacokinetic Report

Statistical analysis

Treatment	90% Confidence Intervals	Point estimate (Flexicam relative to Metacam)
$AUC_{(0-\infty)}$	0.86 – 1.08	0.97
C_{max}	0.88 – 1.04	0.95
T_{max}	0h, 7h (based on median difference between formulations)	3.5h

$T½_{el}$, K_{el} and CL/F appeared comparable for the 2 treatments, although no statistical confirmation was performed. On single occasions, 2 dogs vomited and 2 other dogs produced loose faeces. No other abnormalities were seen (see comment below).

Conclusion

Since the confidence intervals for the parameters $AUC_{(0-\infty)}$ and $C_{max(obs)}$ were within the acceptance range 0.8 – 1.25, the Study Report concludes that Flexicam is bioequivalent to the reference product, Metacam, when administered to dogs.

Median estimates of $T_{max(obs)}$ were also equivalent, although the confidence intervals were relatively wide. A large interanimal variability for meloxicam has been reported previously [Ref 3]. Similarities in $T½_{el}$ and CL/F indicate that there were no differences in kinetics with the two formulations.

Meloxicam shows linear kinetics, as stated in the SPC for the reference product, Metacam.

A single dose study is more likely to detect differences in rate of drug absorption, but not the extent. At steady state, part of the measured drug originates from accumulated drug and does not reflect only the contribution of the last dose administration. The presented conclusions, supported by a number of published studies and kinetic modelling, are that, even for drugs which may accumulate (by implication - at different rates), a single dose study is preferable because the differences in plasma concentrations between formulations will progressively decrease with repeated administrations. It was also considered that use of the loading dose as administered in the single dose study allows for the conclusion of bioequivalence without the need for an additional study at steady state, given that the two parameters AUC and C_{max} are statistically bioequivalent and T_{max} is not considered a pivotal parameter.

The omission of a multiple dose study was therefore adequately justified.

Graphical representations have been provided for mean plasma concentrations and for individual dog. It is evident that there is no consistent pattern of differences between the concentration/time curves for the two formulations.

The CVMP Guideline requires that both the product to be tested and the reference product will be shown to meet all compendial or other applicable standards of identity, strength, quality and purity. As the reference product is an authorised veterinary medicinal product and was commercially obtained, it can be assumed to have attained EU standards of identity, strength, quality and purity.

Although administration was not with food, as recommended in the proposed posology for the product, it was satisfactory for the purposes of this study. Treatments were administered 30 minutes after feeding, when it could be expected that food would still be in the stomach (normally gastric emptying begins immediately but is not usually complete for 3 hours). The choice of administration by syringe enabled the precise dose to be accurately delivered, and administration was consistent between the 2 groups.

Four transient incidents of mild gastrointestinal disturbances (single occurrences of vomiting or loose faeces) were reported; these were noted approximately 5 – 7 days after treatment and involved 3 dogs treated with Flexicam and 1 treated with Metacam. These incidents are unlikely to have been associated with treatment in view of the time delay between treatment and the onset of signs. Nevertheless, in view of the fact that such effects are known to occur with NSAIDs, a suitable warning has been included in the SPC and product literature.

Toxicological studies
Oral suspension
As generic status 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.

Solution for injection
As generic status 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.

User Safety

Inherent Toxicity

As Flexicam is bioequivalent to Metacam the potential impact of the active substance in respect of user safety will be the same for both products.

Exposure of the user

For both formulations, the possible routes of exposure will be the same as those considered for the respective reference products.
It is noted that both formulations will only be used subject to prescription by a veterinary surgeons.

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

In the case of the oral suspension:

- 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 leaflet or the label to the physician.

And for the solution for injection:

- Accidental self-injection may give rise to pain.
- People with known hypersensitivity to NSAID's should avoid contact with the veterinary medicinal product.
- In case of accidental self administration, seek medical advice immediately and show the package leaflet or the label to the physician.

Ecotoxicity
Phase I Assessment
The Applicant refers to the VICH decision tree as presented in the Guideline on Environmental Impact Assessment (EAIs) for Veterinary Medicinal Products – Phase 1 (CVMP/VICH/592/98-FINAL).

A positive answer is given to Question 1 ('Is the VMP exempt from the need for an EIA by legislation and/or regulation?') in view of the provisions of Annex 1 of Directive 2001/82/EC. In this Annex (paragraph 5.2 of Part 3, Chapter 1) it is indicated that an assessment of eco-toxicity is not compulsory for applications submitted in accordance with Article 13 (1).In the case of this product, which is intended for use in individual companion animals, it is accepted that there is no concern relating to environmental risk.

The Phase 1 assessment therefore stops at Question 1.

4. EFFICACY ASSESSMENT

The application is presented in accordance with Article 13 of Directive 2001/82/EC, as amended by Directive 2004/28/EC (that is, a generic application). For Flexicam Oral Suspension, the reference veterinary medicinal product is Metacam 1.5 mg/ml Oral Suspension for Dogs (Boehringer Ingelheim Vetmedica). For Flexicam Solution for Injection, the reference veterinary medicinal product is Metacam 5mg/ml Solution for Injection for Dogs and Cats.

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.

As generic status was confirmed, the results of toxicological and pharmacological tests and clinical trials were not required.

For the Oral Suspension, both Metacam and Flexicam were well tolerated when administered to dogs at the recommended dose rate during the bioequivalence study. Transient mild gastrointestinal signs were seen in both groups. For the Solution for Injection, given that exemption from the requirement for bioequivalence studies can be accepted, the safety profile of Flexicam in the target animal can be assumed to be the same as that for the reference product.

Given that, for both formulations, the safety profile is comparable to Metacam, 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. Flexicam 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.

5. RISK BENEFIT ASSESSMENT

Oral suspension

Flexicam 1.5 mg/ml oral suspension has been formulated as a generic of Metacam 1.5 mg/ml oral suspension. Flexicam contains the same active substance (meloxicam) and preservative (sodium benzoate), in the same concentration as the originator product. The product is a slightly viscous aqueous suspension. The product is presented in white opaque HDPE/LDPE 10 ml, 32 ml and 100 ml multidose bottles. The bottles are fitted with a dropper nozzle which is used to dispense product for small breeds. For larger dose volumes a standard oral dosing syringe is supplied with each pack (dosage is 0.2 mg/kg on the first day with a maintenance dose of 0.1 mg/kg). The Applicant has compared the impurity profile of two batches with that of two batches of the originator and found them to be comparable.

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

a) the bioequivalence between the two products;
b) a satisfactory impurity profile of meloxicam in Flexicam;
c) the contention that the excipients are used in human medicinal products and commonly used in oral suspensions;
d) the fact that a comparable safety profile was obtained with both products in the bioequivalence study.

Target animal and user safety warnings are the same as those for the reference product. Flexicam is exempt from the need for an Environmental Impact Assessment

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.

Flexicam 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 generic status to the reference product, Metacam, by confirmation of bioequivalence between the two products when administered as recommended to the target species, dogs.

The indications and posology as authorised for the reference product can be applied to Flexicam 1.5mg/ml Oral Suspension. The agreed therapeutic indications are:

Dogs:
Alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders.

Solution for injection

Flexicam 5 mg/ml solution for injection has been formulated as a generic of Metacam solution for injection. Flexicam contains the same active substance (meloxicam) and preservative (ethanol), in the same concentrations as the originator product. The product is a clear yellow solution. It is presented in clear Ph. Eur. Type I multidose glass vials of 10 ml. The vials are fitted with an EPDM rubber closure and have an aluminium flip-off seal. The Applicant has provided information about the

impurity profile of the reference product and a comparison of the impurity profile of Flexicam with that of the reference product indicates that the levels of impurities in both products are comparable.

Commitments were provided relating to the specification of a residual solvent, an analytical certificate for meglumine and a diagrammatic representation of one of the packaging components.

Based on information provided, Flexicam 5mg/ml Solution for Injection for Dogs and Cats is considered bioequivalent to the respective reference product. Consequently, it is accepted that the safety and efficacy profiles of the test and reference products will be the same.

It is accepted that Flexicam 5mg/ml Solution for Injection has an acceptable safety profile in the target species when administered at the recommended treatment dose.

It is accepted that Flexicam 5mg/ml Solution for Injection does not represent an unacceptable risk to users or the environment when used in accordance with label instructions.

The indications and posology as authorised for the reference product can be applied to Flexicam 5mg/ml Solution for Injection. The agreed therapeutic indications are:

Dogs:
Alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders.
Reduction of post-operative pain and inflammation following orthopaedic and soft tissue surgery.

Cats:
Reduction of postoperative pain after ovariohysterectomy and minor soft tissue surgery

The benefit: risk assessment is positive.