SCIENTIFIC DISCUSSION

I. SUMMARY OF THE DOSSIER

Loxicom is 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, 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.

Loxicom oral suspension for dogs is indicated 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 or directly into the mouth and measured using a measuring syringe as supplied with the product.

Loxicom 0.5 mg/ml oral suspension for cats is indicated for the alleviation of inflammation and pain in chronic musculo-skeletal disorders in cats. Initial treatment is a single dose of 0.1 mg meloxicam/kg bodyweight on the first day. Treatment is to be continued once daily by oral administration (at 24 hour intervals) at a maintenance dose of 0.05 mg meloxicam/kg bodyweight. The product is to be administered with food or directly into the mouth and can be measured using the measuring syringe provided in the package.

Loxicom solution for injection for dogs and cats is indicated in dogs for the alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders and reduction of post-operative pain and inflammation following orthopaedic and soft tissue surgery and in cats for the reduction of post-operative pain after ovariohysterectomy and minor soft tissue surgery. 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.

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

2. QUALITY ASSESSMENT

Composition of the Veterinary Medicinal Product

Loxicom oral suspension for dogs contains meloxicam as active substance and is presented in two strengths: 0.5 mg/ml and 1.5 mg/ml meloxicam. It was confirmed that Loxicom 0.5 mg/ml oral suspension for cats is identical to Loxicom 0.5 mg/ml oral suspension for dogs. Loxicom solution for injection for cats and dogs contains 5 mg/ml meloxicam. Conventional pharmaceutical excipients are used and details are included in the Summary of Product Characteristics (SPC).

Containers

0.5 mg/ml oral suspension for dogs
The product is presented in 15 ml and 30 ml polyethylene screw bottles with HDPE/LDPE child resistant caps. Two polyethylene /polypropylene measuring syringes are supplied with each bottle to ensure accurate dosing of small and large dogs, a 1 ml and a 5 ml syringe. Each syringe is graduated in bodyweight, the 1 ml syringe is graduated from 0.25 kg to 5.0 kg and the 5 ml syringe from 1 kg to 25 kg.

0.5 mg/ml oral suspension for cats
The product is presented in a 15 ml polyethylene screw bottle with a HDPE/LDPE child resistant cap and measuring syringe. The 1 ml measuring syringe fits onto the bottle and has a kg-body weight scale for cats (0.5 to 10 kg) which corresponds to the maintenance dose. Thus for initiation of the therapy on the first day, twice the maintenance volume is required.

1.5 mg/ml oral suspension for dogs

The product is presented in 10 ml, 32 ml and 100 ml polyethylene screw bottles with HDPE/LDPE child resistant caps. Two polyethylene/ polypropylene measuring syringes are supplied with each bottle to ensure accurate dosing of small and large dogs, a 1 ml and a 5 ml syringe. Each syringe is graduated in bodyweight, the 1 ml syringe is graduated from 0.5 kg to 15 kg and the 5 ml syringe from 2.5 kg to 75 kg.

5 mg/ml solution for injection for dogs and cats

The product is presented in 10 ml, 20 ml and 100 ml clear glass vials with bromobutyl bungs and aluminium seals.

Development Pharmaceutics

Oral suspension

The product has been formulated to be essentially similar to the reference product Metacam oral suspension. The product contains meloxicam at a concentration of 0.5 mg/ml and 1.5 mg/ml and is presented as an oral suspension. The product has also been formulated to contain the preservative sodium benzoate at a concentration of 1.5 mg/ml. This is the same preservative system used in the reference product. Preservative efficacy has been demonstrated.

The excipients used in this formulation are widely used in pharmaceutical products and the role of each in the formulation was described. The appropriate pH range was determined based on that of the reference product. In order to help establish essential similarity, the impurity profile of the Loxicom and Metacam were compared. The impurity details provided demonstrate that the test product has a comparable profile to that of the reference product.

The packing material was chosen with consideration to that of the reference product and satisfactory stability data were presented. Loxicom oral suspension is supplied with a dosing device and a dose delivery test has been carried out on each syringe at the lowest and highest point of the scale. All results comply with Ph. Eur. requirements for uniformity of mass of delivered dose from multidose containers.

Solution for injection

The product has been formulated to be essentially similar to the reference product Metacam 5 mg/ml solution for injection for dogs and cats and is comparable qualitatively and quantitatively with the reference product. The product contains Meloxicam at a concentration of 5 mg/ml and is presented as a solution for injection. The product has also been formulated to contain the preservative ethanol at a concentration of 150 mg/ml. This is the same preservative system used in the reference product. Preservative efficacy has been performed.

The excipients used in this formulation were selected based on those in the reference product and the role of each in the formulation is described. In order to help establish essential similarity, the impurity profile of Loxicom and Metacam were compared. The impurity details provided demonstrate that Loxicom has a comparable profile to that of the reference product Metacam. The packing material was also chosen with consideration to that of the reference product. Satisfactory stability data were presented. Results were provided demonstrating the suitability of the closures for use in these multidose products.

METHOD OF MANUFACTURE

Manufacturing Formula and Batch Size

Oral suspension

The manufacturing formulation was presented for each batch size proposed for the 0.5 mg/ml suspension and 1.5 mg/ml suspension.

Solution for injection

The manufacturing formulation was presented for the proposed batch size.

Manufacturing Process and In-process Controls

Oral suspension

Manufacture involves the preparation and combination of a number of solutions/suspensions. Mixing speeds are specified and in-process control detailed.

Solution for injection

Details of the manufacturing process are provided, including on dissolution of individual components, mixing speeds and mixing times, how the solution is made up to volume, filled into vials and sterilised.

Validation of Manufacturing Process

Oral suspension

Process validation data was presented. Critical parameters were monitored throughout the process and the data presented was satisfactory.

Solution for injection

Process validation data was presented. Critical parameters were monitored throughout the process and the data presented was satisfactory.

CONTROL OF STARTING MATERIALS

Active Substance

A Drug Master File (EDMF) for the active substance meloxicam was provided with all relevant data for the raw material. The active substance complies with the British Pharmacopoeia monograph and additional in-house tests and limits were described.

Analytical methods and validation

Assay of meloxicam is determined using the British Pharmacopoeia titration method. Related substances are also determined using the method described in the British Pharmacopoeia. Appropriate validation of this method was provided.

Scientific data

Nomenclature

Nomenclature of the active substance is presented:

Generic name: Meloxicam (INN, BAN)
Chemical Name: 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide
CAS (Chemical Abstract Service) No. : 71125-38-7

Description

Description of the active substance: pale yellow coloured powder
Molecular Formula: $C_{14}H_{13}N_3O_4S_2$
Molecular Weight: 351.41

Quality control during manufacture

Appropriate quality control is carried out and satisfactory specifications were provided.

Development Chemistry

The development chemistry was presented.

Evidence of structure

The chemical structure has been shown analytically by UV, IR, MS, ^{1}HNMR, ^{13}CNMR and elemental analysis. Satisfactory spectra and interpretation were provided. The route of synthesis also confirms the structure of meloxicam.

Physico-chemical characterisation

The solubility is described in the British Pharmacopoeia monograph. Polymorphic form I is routinely produced and this is confirmed by IR spectral absorbance. No literature describes isomerism for meloxicam.

Impurities

Meloxicam is tested in accordance with the British Pharmacopoeia. Potential known impurities were identified.

Residual solvents

Solvents used in the manufacture of meloxicam and potentially present in the raw material were listed which are limited in line with EU/VICH limits (see EMEA/CVMP/511/03 annexes to CVMP/VICH/502/99 Guideline on Impurities: Residual Solvents).

Batch analysis

Satisfactory batch data was provided for pilot scale and full scale batches. All tests listed on the specification were reported and all results were within specification.

Excipients

Excipients described in a Pharmacopoeia

Oral suspension

All excipients are tested according to their corresponding monograph. Specifications and typical supplier's certificates of analysis were provided for all excipients.

Solution for injection

All excipients are tested according to their corresponding monograph. Specifications and typical supplier's certificates of analysis were provided for all excipients.

Excipient(s) not described in a Pharmacopoeia

Glycofurol (solution for injection): Glycofurol is not a new excipient as it is used in other authorised veterinary medicinal products within the EU. The specification for glycofurol is adequate and includes relevant parameters. A typical certificate of analysis from the supplier, demonstrating compliance with the specification was provided. Methods of analysis were also provided for this excipient.

Packaging Material (Immediate Packaging)

0.5 mg/ml oral suspension for dogs

The product is presented in 15 ml and 30 ml polyethylene terephtalate (PET) screw bottles with HDPE/LDPE child resistant caps. Two polyethylene / polypropylene measuring syringes are supplied with each bottle to ensure accurate dosing of small and large dogs, a 1 ml and a 5 ml syringe. Each syringe is graduated in bodyweight, the 1 ml syringe is graduated from 0.25 kg to 5.0 kg and the 5 ml syringe from 1 kg to 25 kg. Compliance with relevant Ph. Eur. monographs and/or food contact requirements are certified for the various components.

0.5 mg/ml oral suspension for cats

The product is presented in a 15 ml polyethylene screw bottle with a HDPE/LDPE child resistant cap and measuring syringe. This measuring device is unique to the cat product (that is, it is a different size to the measuring devices supplied with Loxicom 0.5 mg/ml oral suspension for dogs). The measuring device is a 1 ml measuring syringe with a kg-body weight scale for cats of 0.5 to 10 kg. The Applicant has carried out an assessment of uniformity of mass of delivered doses using the proposed measuring syringe in accordance with Ph. Eur. 2.9.27 'Uniformity of mass of delivered doses from multidose containers'. Accuracy of the syringe at the lowest and highest dose was determined and results are in compliance with the monograph.

1.5 mg/ml oral suspension for dogs

The product is presented in 10 ml, 32 ml and 100 ml polyethylene terephtalate (PET) screw bottles with HDPE/LDPE child resistant caps. Two polyethylene / polypropylene measuring syringes are supplied with each bottle to ensure accurate dosing of small and large dogs, a 1 ml and a 5 ml syringe. Each syringe is graduated in bodyweight, the 1 ml syringe is graduated from 0.5 kg to 15 kg and the 5 ml syringe from 2.5 kg to 75 kg. Compliance with relevant Ph. Eur. monographs and/or food contact requirements are certified for the various components.

5 mg/ml solution for injection for dogs and cats

The product is to be presented in 10 ml, 20 ml and 100 ml vials. The vials are composed of clear Ph. Eur. Type 1 glass. The 20 mm rubber stoppers are composed of grey bromobutyl and there is a 20 mm aluminium flip-off seal. Declarations of compliance with Ph Eur requirements for type I glass are provided for all three vial sizes. The bromobutyl rubber bungs are certified as complying with Ph Eur requirements including penetrability, fragmentation and self sealing. Broaching studies in excess of the number of broachings likely to occur in practice have also been conducted.

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

Declarations were provided from all manufacturers of the starting materials that no input materials used for the production of the finished product fall within the scope of the guidance "Note for guidance on minimising the risk of Transmitting animal Spongiform Encephalopathy agents via Human and Veterinary Medicinal Products" (EMEA/410/01-Rev.2).

Control Tests on Finished Product

Product Specification and Routine Tests:

The finished product release and shelf life specifications were provided for both the oral suspension and solution for injection forms of the product. Test procedures for identification and quantitative determination for the active substance and identification and determination of excipients were described. Other tests on the specification are appropriate for the respective dosage forms.

Scientific Data

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

Oral suspension

The analytical methods for assay, related substances and preservatives have been validated in line with VICH requirements. The method for determination of microbial quality has been validated in line with Ph Eur requirements for both product strengths of the oral suspension.

Solution for injection

The analytical methods for assay, related substances and preservatives have been validated in line with VICH requirements. The sterility method has been validated in line with Ph Eur requirements.

Batch analysis

Batch data were presented and results were within specification.

Stability

Stability Tests on the Active Substance

Data for the final active substance under VICH conditions has been conducted for a number of pilot scale batches (up to 9 months at 25 ˚C/60% RH and 40 ˚C/75% RH) and production scale batches (up to 12 months at 25 ˚C/60% RH and 6 months at 40 ˚C/75% RH)).

The data was satisfactory to support the proposed retest period of 24 months.

Stability Tests on the Finished Product

Product Specification and Routine Tests for shelf life:

The shelf life specifications were described.

Stability Tests

0.5 mg/ml oral suspension

The proposed shelf life of 18 months with no specific storage precautions was accepted based on the data provided.

1.5 mg/ml oral suspension

The proposed shelf life of 18 months with no specific storage precautions was accepted based on the data provided.

Photostability

A photostability study was conducted on a pilot scale batch of each strength of the oral suspension. No significant changes were observed and a storage precaution to protect from light is not required for the product.

Solution for injection

The proposed shelf life of 18 months with no specific storage precautions was accepted based on the data provided.

Photostability

A photostability study was conducted on two pilot scale batches. No significant changes were observed and a storage precaution to protect from light is not required for the product.

In-use Stability Tests

Oral suspension

A satisfactory in-use study was conducted on production scale batches of both product strengths confirming an in-use shelf life of 6 months. Broaching conditions satisfactorily mimicked use of the product in the field. The study will be repeated with product at the end of shelf life, when available.

Solution for injection

A satisfactory in-use study has been conducted on a pilot scale and a production scale batch confirming an in-use shelf life of 28 days. Broaching conditions satisfactorily mimicked use of the product in the field. The study will be repeated with product at the end of shelf life, when available.

3. SAFETY ASSESSMENT

As bioequivalence to appropriate reference products 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.

Pharmacodynamics

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

Toxicological studies

As bioequivalence to appropriate reference products was confirmed and in accordance with Article 13 (1) of Council Directive 2001/82/EC, as amended by Directive 2004/28/EC, the toxicological profile of meloxicam does not need to be reassessed.

Tolerance in the target species of animal

A tolerance study was conducted in dogs (oral suspension and solution for injection) and in cats (solution for injection). The studies showed that the product was well tolerated.

In support of the application for the 0.5 mg/ml oral suspension for cats the applicant has conducted a target animal safety study in cats to evaluate the safety of administration of Loxicom 0.5 mg/ml oral suspension for cats under clinical conditions. This allowed to conclude that the safety profile of this product will be similar to that of the authorised reference product and that the adverse effects that could potentially be associated with the use of this product are adequately detailed in section 4.6 of the SPC.

Reproductive toxicity, including teratogenicity

The application was made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application, and therefore no data were presented.

Studies of other effects

Special studies

The application was made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application, and therefore no data were presented.

Observations in humans

The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application, and therefore no data were presented.

Microbiological studies (studies on human gut flora and organisms used in food processing)

Reference was made to the MRL summary report for Meloxicam.

Studies on the microbiological properties were not submitted, as it was not considered necessary in view of the nature of the compound.

Studies on metabolites, impurities, other substances and formulation

Oral suspension

The excipients used in Loxicom oral suspension for dogs are well established and have an extensive history of use as excipients in food and pharmaceutical products at concentrations comparable to those specified in this product. Given the known use of the excipients it is not expected that they will present a hazard to either the target animal or the user.

It has been confirmed that Loxicom 0.5 mg/ml oral suspension for cats is chemically, pharmaceutically and biologically identical (same formulation) to Loxicom 0.5 mg/ml oral suspension for dogs.

Solution for injection

The excipients used in Loxicom solution for injection for dogs and cats are well established and have an extensive history of use in parenteral preparations at concentrations comparable to those specified in this product. Given the known use of the excipients, it is not expected that they will present a hazard to either the target animal or the user.

User Safety

Inherent Toxicity

As Loxicom 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 the oral suspension, the possible routes of exposure (dermal, oral, and ocular) for the active ingredient and the excipients were reviewed and reference was made to published literature relating to human exposure to the active ingredient and the excipients. The product will be administered by veterinary surgeons or dog owners. Veterinary surgeons will be skilled in administering such a product and dog owners will usually be capable of administering such products but may, if necessary, consult the product literature or their veterinary surgeon.

The product will be supplied at two different concentrations and a 1ml and 5ml syringe will be supplied with each formulation. As a precaution against the incorrect syringe being used to dispense the relevant formulation, the syringes and the packaging will be colour coded. Adequate safety information was provided relating to the potential for ingestion of the product by a child.

It was confirmed that Loxicom 0.5 mg/ml oral suspension for cats is chemically, pharmaceutically and biologically identical (same formulation) to Loxicom 0.5 mg/ml oral suspension for dogs. In addition, the vial size of 15 ml is the same as that of Loxicom 0.5 mg/ml oral suspension for dogs. It is accepted that use of this formulation for the treatment of cats will not put the user at any greater risk compared to when the formulation is used for the treatment of dogs. Furthermore, the volume of product for administration to cats will typically be less than that required to treat dogs. Therefore, user exposure to the formulation is expected to be less for Loxicom 0.5 mg/ml oral suspension for cats compared to potential user exposure for Loxicom 0.5 mg/ml oral suspension for dogs. The proposed user safety warnings are considered appropriate.

For the solution for injection, the possible routes of exposure (dermal, oral, ocular and parenteral) for the active ingredient and the excipients were reviewed and reference was made to published literature

relating to human exposure to the active ingredient and the excipients. The product will be administered by veterinary surgeons or veterinary nurses who will be skilled in administering such a product.

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.

Environmental Risk Assessment

Phase I Assessment

An environmental risk assessment was provided in compliance with VICH GL6 (Environmental impact assessment for veterinary medicinal products – Phase I)
Given that the product is:

- for non-food producing species
- for treatment of individual animals

the product will produce environmental exposures well below concentrations that impact on the environment and therefore the environmental risk assessment stops at Phase I.

The disposal advice proposed is the same as for Metacam:

'Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements'.

4. EFFICACY ASSESSMENT

Pharmacokinetics

Oral suspension

Absorption

Meloxicam is completely absorbed following oral administration and maximal plasma concentrations are obtained after approximately 7.5 hours. When the product is used according to the recommended dosage regime, steady state concentrations of meloxicam in plasma are reached on the second day of treatment.

Distribution

There is a linear relationship between the dose administered and plasma concentration observed in the therapeutic dose range. Approximately 97% of meloxicam is bound to plasma proteins. The volume of distribution is 0.3 l/kg.

Metabolism

Meloxicam is predominantly found in plasma and is also a major biliary excretion product whereas urine contains only traces of the parent compound. Meloxicam is metabolised to an alcohol, an acid derivative and to several polar metabolites. All major metabolites have been shown to be pharmacologically inactive.

Elimination

Meloxicam is eliminated with a half-life of 24 hours. Approximately 75% of the administered dose is eliminated via faeces and the remainder via urine.

Demonstration of bioequivalence

In support of the application for the oral suspension for dogs, a report was presented on a study conducted in dogs for the purposes of comparing the plasma pharmacokinetic profile following the administration of the test product (Loxicom 1.5mg/ml oral suspension for dogs) with the plasma pharmacokinetic profile following administration of the reference product (Metacam 1.5mg/ml oral suspension for dogs). 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-FINAL). Based on the ratios of the treatment means for AUC and Cmax, it is accepted that the two products can be considered bioequivalent.

In addition to the *in vivo* bioequivalence study, a dissolution study was conducted to compare the rate and extent of dissolution of Loxicom 1.5mg/ml and Loxicom 0.5mg/ml, with Metacam oral suspension for dogs 1.5mg/ml and Metacam oral suspension for dogs 0.5mg/ml. The study was conducted according to the 6th edition of the European Pharmacopeia and analysis of all *in-vitro* samples was performed using UV spectrophotometric methodology as detailed in the USP monograph for Meloxicam oral suspension.

The product was considered very rapidly dissolving and deemed equivalent without a profile comparison. For the other two test media, the dissolution profile of Loxicom oral suspension 0.5 mg/ml was deemed similar to those of both Metacam oral suspension 0.5mg/ml and Loxicom oral suspension 1.5 mg/ml. Based on the available dissolution data, it is accepted that Loxicom 0.5 mg/ml and Metacam 0.5 mg/ml oral suspensions can be considered bioequivalent.

Similarly in support of the application for the 0.5 mg/ml oral suspension for cats, the applicant has conducted a single *in-vivo* bioequivalence study in order to demonstrate that the test product (Loxicom 0.5 mg/ml oral suspension for cats) and the reference product (Metacam 0.5 mg/ml oral suspension for cats) are bioequivalent. Based on the findings of this study, bioequivalence has been demonstrated. It can be accepted that the efficacy profile of the product will be the same as that of the reference product Metacam 0.5 mg/ml oral suspension for cats.

Solution for injection

Absorption

Following subcutaneous administration, meloxicam is completely bioavailable and maximal mean plasma concentrations of 0.73 µg/ml in dogs and 1.1 µg/ml in cats were reached approximately 2.5 hours and 1.5 hours post-administration, respectively.

Distribution

There is a linear relationship between the dose administered and plasma concentration observed in the therapeutic dose range in dogs. More than 97% of meloxicam is bound to plasma proteins. The volume of distribution is 0.3 l/kg in dogs and 0.09 l/kg in cats.

Metabolism

In dogs, meloxicam is predominantly found in plasma and is also a major biliary excretion product whereas urine contains only traces of the parent compound. Meloxicam is metabolised to an alcohol, an acid derivative and to several polar metabolites. All major metabolites have been shown to be pharmacologically inactive.

Elimination

Meloxicam is eliminated with a half-life of 24 hours in dogs and 15 hours in cats.
Approximately 75% of the administered dose is eliminated via faeces and the remainder via urine.

Demonstration of bioequivalence

The application for a marketing authorisation for Loxicom was in accordance with the 'Guideline for the conduct of Bioequivalence studies for Veterinary Medicinal Products' (EMEA/CVMP/016/00-FINAL) and fulfils point '4b' of the exemptions from the need for bioequivalence studies. 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'.
> ……

Furthermore, reference was made to the (Human) Notice for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), section 5.1.6, Parenteral Solutions, which states:

> 'In the case of other parenteral routes, e.g. intramuscular or subcutaneous, if the product is of the same type of solution (aqueous or oily), contains the same concentration of the same or comparable excipients as the medicinal products currently approved, then bioequivalence testing is not required'.

It was claimed that Loxicom 5mg/ml injection is identical in formulation to Metacam 5mg/ml Solution for Injection for Dogs and Cats, in terms of active substance and excipients and therefore in this instance bioequivalence studies are not required. Based on the data provided, it was accepted that the claimed exemption applies.

5. BENEFIT RISK BALANCE

In the case of Loxicom 0.5 mg/ml and 1.5 mg/ml oral suspension for dogs these products have been formulated as generics of the reference product Metacam. Loxicom contains the same active substance (meloxicam) and preservative (sodium benzoate), in the same concentration as the originator product. Comparison of the impurity profile of Loxicom with that of the reference product indicated that the levels of impurities in both products are comparable.

Loxicom solution for injection for dogs and cats has been formulated as a generic to Metacam solution for injection. Loxicom contains the same active substance (meloxicam) and preservative (ethanol), in the same concentrations as the originator product. Comparison of the impurity profile of Loxicom solution for injection for dogs and cats with that of the reference product indicated that the levels of impurities in both products are comparable.

Based on *in vivo* and *in vitro* data provided, Loxicom 0.5 mg/ml oral suspension for dogs and Loxicom 1.5 mg/ml oral suspension for dogs and Loxicom 5 mg/ml solution for injection for dogs and cats are considered bioequivalent to the respective reference products. Consequently, it is accepted that the safety and efficacy profiles of the test and reference products will be the same. Based on the findings of several target animal safety studies it is accepted that the test products have an acceptable safety profile in the target species when administered at the recommended treatment dose.

Loxicom 0.5 mg/ml oral suspension for cats contains 0.5 mg meloxicam per ml and bioequivalence with the reference product Metacam 0.5 mg/ml oral suspension for cats has been accepted. Given that bioequivalence with the reference product is accepted, the efficacy profile in cats can be expected to be similar to that of the reference product.

For all formulations, it is accepted that they do 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 products can be applied to the test products.

The products are manufactured in Northern Ireland by Norbrook Laboratories Limited. The site is authorised in compliance with EU GMP requirements. The manufacture and control of the products is in accordance with current guidelines and the shelf life and storage precautions detailed in the SPCs are supported by appropriate stability data.

The application for a marketing authorisation for Loxicom was made in accordance with Article 13 (1) of Directive 2001/82/EC as amended. 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 products were considered to be in accordance with Directive 2001/82/EC as amended.