SCIENTIFIC DISCUSSION

MELOXIDYL 1.5 MG/ML ORAL SUSPENSION FOR DOGS AND MELOXIDYL 5MG/ML SOLUTION FOR INJECTION FOR DOGS AND CATS

1. SUMMARY OF THE DOSSIER

The application concerns MELOXIDYL, 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 shall not be 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.

An extension for a new pharmaceutical form solution for injection 5mg/ml for dogs and cats was granted for MELOXIDYL in September 2009. The new pharmaceutical form, solution for injection 5mg/ml for dogs and cats, has been formulated to be pharmaceutically equivalent to the reference product Metacam.

For MELOXIDYL 5mg/ml 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 of bodyweight and MELOXIDYL 1.5 mg/ml oral suspension may be used for continuation of treatment at a dosage of 0.1 mg meloxicam/kg body weight, 24 hours after administration of the injection. For the reduction of post-operative pain (over a period of 24 hours) the recommended posology for dogs is a single intravenous or subcutaneous injection at a dosage of 0.2 mg meloxicam/kg body weight before surgery, for example at the time of induction of anesthesia. In cats the recommended posology for the reduction of post-operative pain is a single subcutaneous injection of 0.3 mg meloxicam/kg of body weight before surgery for example at the time of induction of anesthesia.

2. QUALITY ASSESSMENT

Composition of oral suspension 1.5mg/ml for dogs

Qualitative Composition	Quantitative composition (mg/ml)
<u>*Active Substance*</u> Meloxicam	1.5
<u>*Other ingredients*</u> Xanthan gum Silica, colloidal anhydrous Sorbitol liquid (non-crystallising) Glycerol 85%	

Xylitol Sodium benzoate Citric acid anhydrous Purified water	2.0

Composition of solution for injection 5mg/ml for dogs and cats

Qualitative Composition	Quantitative composition (mg/ml)
Active Substance Meloxicam	5.0
Other ingredients Ethanol anhydrous* Poloxamer 188 Glycofurol Meglumine Glycine Sodium chloride Sodium hydroxide Water for injections	150.0

Container

Oral suspension
Polyethylene screw bottles 10 ml, 32 ml and 100 ml. All bottles have the same tamper-evident screw cap fitted with a syringe insert. The syringe insert is clipped inside the cap. The bottles and caps are of white high density polyethylene. The syringe inserts are made of low density polyethylene. The syringes are made of transparent polypropylene.

Two syringes (0.5 ml and 5 ml) are available with each presentation. The syringes are graduated in kg body weight. The 0.5 ml syringe is graduated every 0.5 kg until 7 kg and the 5 ml syringe is graduated every 2.5 kg until 70 kg.

Solution for injection
Clear Ph. Eur Type 1 glass vial 10ml with 20mm grey Ethylene Propylene Diene Monomer (EPDM) rubber stopper with a 20 mm Aluminium flip-off violet coloured seal.

Clinical Trial Formula(e)

For the oral suspension the composition used during the bioequivalence studies is identical to that presented above.

For the solution for injection MELOXIDYL and Metacam solutions for injection were accepted to be bioequivalent as they have:

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

Development Pharmaceutics

The aim of the development studies was to develop an oral suspension essentially similar to the reference product Metacam 1.5 mg/ml oral suspension for dogs. The composition is mainly based on the composition of the reference product.

Meloxicam in the British Pharmacopoeia (BP) is described as a pale yellow powder, practically insoluble in water, slightly soluble in acetone, soluble in dimethylformamide, very slightly soluble in ethanol and in methanol. As for the reference product meloxicam is micronized, specified particle size is below 30 µm.

The aim was to formulate a product with physico-chemical properties as closely as possible related to the reference product. A formulation with Xanthan gum 0.2 % was chosen. This concentration was found to have similar viscosity properties as the reference product Metacam. The choice of silica colloidal anhydrous is based on the formula for Metacam.

The same preservative as used in the reference product sodium benzoate was chosen. The concentration was determined after challenge tests (according to Ph. Eur.) performed with different concentrations of sodium benzoate. The method was validated according to Ph. Eur. A concentration of 0.20% was selected to assure a safety margin. A reduction of the concentration due to degradation during the finished product shelf-life down to 0.15% was shown to be efficient.

The same sweetening agents as used in Metacam oral suspension were used. In order to mask the bitter taste a flavouring agent, vanilla aroma was tested. The performed palatability studies proved that there was no difference with or without vanilla aroma. Accordingly no flavouring agent is added. The same pH as used in Metacam oral suspension was selected. Citric acid was chosen as a pH adjuster.

The packages have been selected on the basis of the packages approved for the reference product. Polyethylene screw bottles 10 ml, 32 ml and 100 ml. All bottles have the same closure, a tamper-evident screw cap fitted with a syringe insert. Two syringes are available with each presentation, graduated in kg body weight of dog: one 0.5 ml syringe graduated every 0.5 kg until 7 kg and one 5 ml syringe graduated every 2.5 kg until 70 kg. Two batches in the chosen packages have been stability tested for up to 6 months at 25ºC/60% RH and at 40 ºC/75% RH. Tested parameters were appearance, density, pH, viscosity, meloxicam assay, sodium benzoate assay and microscopic examination (appearance and particle dimension < 30µm). One batch of the reference product Metacam 1.5 mg/ml oral suspension for dogs has also been tested after storage for 6 months at 40 ºC/75% RH. The results were all within the stated limits, no decrease in meloxicam content or in preservative content were noted.

The syringes have been tested for mass uniformity of delivered dose and for content uniformity of delivered dose, both of which were satisfactory.

For the solution for injection the product has been formulated to be pharmaceutically equivalent to the reference product Metacam 5mg/ml solution for injection for dogs and cats and it is stated to be comparable qualitatively and quantitatively with the reference product.

METHOD OF PREPARATION

Manufacturing Formula and Batch Size

For the oral suspension, the manufacturing formulae for the proposed industrial scale batches 500 L, 1000 L, 2000 L, 3000 L and 4000 L have been presented.

For the solution for injection the manufacturing formula for a 50 litre batch size was presented.

Manufacturing Process and In-process Controls

For the oral suspension, the manufacturing process and the in-process controls were specified in a manufacturing process flow chart. A detailed description of each one of the 7 operation steps in the manufacturing process (for a 4000 L batch size) was submitted as was a description of the in-process controls.

The manufacturing process and the in-process controls are described appropriately and are considered adequate.
For the solution for injection, the 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 Manufacturing Process

For the oral suspension, whilst the validation studies performed on pilot batches have demonstrated the adequacy of the manufacturing process, results of validation of industrial scale batches are necessary. A commitment has been provided to complete the validation studies before marketing and a validation scheme has been provided. Validation studies will be performed on three industrial scale batches manufactured at site A and three industrial scale batches manufactured at site B. Results from the validation studies will be submitted to the authorities as soon as available.

For the 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 was principally concerned with establishing / confirming processing times for addition of ingredients during preparation of the bulk solution and was 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

For the manufacture of the oral suspension, meloxicam is supplied from two active substance manufacturers. Complete Active Substance Master Files (ASMFs) were submitted. The quality of the active substance meloxicam conforms to the BP.

For the manufacture of the solution for injection, meloxicam is supplied by a one manufacturer. A complete ASMF was submitted. The quality of the active substance meloxicam complies with the European Pharmacopoeia (Ph. Eur.).

Analytical methods and validation

The GC and HPLC methods used were appropriately validated and the impurities isolated.

Physico-Chemical Characteristics liable to affect biovailability

The solubility was presented and the limits for particle size distribution of the suspended meloxicam were included in the active substance specifications.

Scientific data

The active substance is derived from two manufacturers. The substance supplied is non-micronised. The micronisation step was described in detail.

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:	$C_{14}H_{13}N_3O_4S_2$
Molecular weight:	351.4

Quality control during manufacture

Appropriate quality control is carried out.

Development Chemistry

The development chemistry was presented.

Evidence of structure

The evidence of the chemical structure was verified by methods including Elemental analysis (EA), Mass Spectrum, ^{1}H-NMR and ^{13}C-NMR. In addition HPLC, UV, IR and UV tests have been performed and results provided.

Potential impurities and residual solvents

Oral suspension
Meloxicam is tested in accordance with the BP. Five impurities are listed in BP and a number of them are potential impurities in the manufacturing processes used. The impurity profiles for related substances and residual solvents (acetone, methanol and xylene) were presented and found to be satisfactory.

Solution for injection
Possible impurities which may arise from the route of synthesis and starting material listed in the Ph. Eur. and the possible process impurities from the starting materials were presented. One of the starting materials was identified 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. The degradation products do not co-elute with the meloxicam peak and the assay is therefore considered to be stability indicating. Residual solvents (methanol, methylene dichloride and toluene) were limited in line with the VICH limits.

Batch analysis

For the oral suspension, data from batch analyses performed on 3 batches were presented and all results complied with the proposed specification.

For the solution for injection, batch data were provided for 3 batches. The results presented are within the limits of the proposed specification for meloxicam.

Excipients

Oral Suspension
The excipients included are xanthan gum, colloidal anhydrous silica, sorbitol liquid (non-rystallising), glycerol 85%, xylitol, sodium benzoate, citric acid anhydrous and purified water. All excipients are described in Ph. Eur. and tested in compliance with the requirements in the current Ph. Eur. monographs.

Copies of certificates of analysis for one batch of each one of the excipients are presented. All results were within the stated limits.

Solution for injection
The excipients included which comply with a Pharmacopeia are: ethanol anhydrous, poloxamer 188, meglumine, glycine, sodium chloride, sodium hydroxide, and water for injection. The excipient Glycofurol is not described in a Pharmacopeia, but its specification was considered adequate.

Packaging Material (Immediate Packaging)

Oral suspension
The dimensions and specifications of the bottles, caps and syringes were described and all components met the Ph. Eur. requirements.
Two syringes are available with each presentation. Dose delivery studies have been performed and were assessed under Development Pharmaceutics.

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

SPECIAL MEASURES CONCERNING THE PREVENTION OF TRANSMISSION OF ANIMAL SPONGIFORM ENCEPHALOPATHIES.

The product does not contain any material of animal origin and no material of animal origin is used during the manufacturing process.

CONTROL TESTS ON FINISHED PRODUCT

Product Specification and Routine Tests

The release and shelf- life specifications for MELOXIDYL 1.5 mg/ml oral suspension and MELOXIDYL 5 mg/ml solution for injection were presented.

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

The release specifications do not include determination of related substances. The degradation product level has been determined using the HPLC method adapted from BP. The method was used to control the impurity level during the manufacture from raw material to finished product. Results from 5 batches were presented. The results were all below LOD of 0.1%. Based on these results it was considered acceptable to exclude the purity test from the release specifications. A test for related substances is included in the active substance specification and in the finished product shelf-life specifications.

The description of the methods used for the control of the finished product and the specifications were provided. Determination of the active substance content was carried out using HPLC method detection. Results for all batches were within proposed specifications.

STABILITY

Stability Tests on the Active Substance

Oral suspension
Results from storage of three laboratory scale batches and three pilot scale batches from one active substance manufacturer were presented. The samples were packed in double PE-bags contained in miniature drums (the same as those used to market the product).
Data from storage of the laboratory scale batches up to 24 months at 25°C/60%RH (will continue for up to 60 months) and up to 6 months at 40°C/70%RH are available.
Data from storage of the pilot scale batches up to 12 months at 25°C/60%RH (will continue for up to 60 months) and up to 6 months at 40°C/70%RH are available.

Successively one batch per year will be introduced in normal condition stability studies. Tested parameters have been appearance, related substances (HPLC), loss on drying and assay (potentiometric) in accordance with the specification.

From the second active substance manufacturer, results from storage of commercial scale batches in three programmes were provided. In addition at least one batch will be added to the stability programme for every year irrespective of any changes. Tested parameters have been appearance, related substances (HPLC), loss on drying and assay (potentiometric) in accordance with the specification.

The presented results were within the stated limits. There are no significant changes in appearance, loss on drying or assay either during the stability studies at 25°C/60%RH up to 24 months. No adverse trend was observed at accelerated conditions up to 6 months.

Solution for injection
The long-term stability study at 25°C/60% RH and 30°C/60% RH is scheduled to continue for 60, 66 and 72 months and 1 batch per year will be added to the stability programme. The parameters description, identification by IR, polymorphic identity, related substances, loss on drying and assay, have been followed.

No significant changes were observed in any of the parameters monitored and in any of the mentioned storage conditions and storage time. All parameters remained well within the specification.

A re-test period of 24 months with no specific storage precautions was proposed which is considered acceptable.

Micronised meloxicam

For meloxicam the retest period of 24 months without any specific storage conditions proposed by the finished product manufacturer was considered acceptable based on the submitted stability data. For *micronised* meloxicam the proposed retest period 12 months without any specific storage conditions was considered acceptable based on the submitted stability data.

The stability tests studies performed by one active substance supplier include tests on laboratory and pilot scale batches. The stability studies from this supplier will be performed on production scale batches and a post-approval stability test commitment to perform complementary stability studies on production scale batches was provided.

Stability Tests on the Finished Product

The applicant has discussed the selected Bracketing and Matrixing concept and the reduced design has been appropriately justified.

Long term and accelerated studies

For the oral suspension, parameters studied were appearance, relative density, particle size, pH, homogeneity of suspension, related substances, assay of meloxicam, assay of sodium benzoate and packaging characteristics (appearance and function). Microbiological contamination and challenge test are performed initially and at the end of stability study for samples stored at 25°C, 60 % RH.

All results comply with the specifications. Impurity A, B, C, other impurity and total impurities were below the limit of the detection 0.1% at all tested time points up to 6 months at both conditions studied 25°C, 60 % RH and 40°C, 75 % RH. The 25°C, 60 % RH study is on-going and will continue for up to 36 months.

For the solution for injection, results up to the time points identified were presented for all batches stored under long-term and accelerated conditions and for the control study (2-8°C).

For the pH specification, results reported for all batches across all storage conditions (40°C / 75%RH, 25°C / 60%RH) are within the range pH 8.29 – 8.7.

Stability results for assay of the active substance for all three batches across all storage conditions are within the range 94.7% to 101.1%. As with the pH specification, the data indicates that the various storage conditions have no impact on assay results e.g. at 40°C / 75%RH results for assay are in the range 96.2%-100.1%, at 25°C / 60%RH results for assay are in the range 94.7%-99.8%, at 2-8°C results for assay are in the range 95.4%-101.1%.

Photostability test

For the oral suspension, the test was performed on two batches of finished product and one batch of meloxicam. The light source, in accordance with current guidelines provided an overall illumination of 1.2 million lux. Parameters studied were appearance, relative density, external and internal appearance of packaging (samples stored in packages intended for marketing), related substances, assay of meloxicam and assay of sodium benzoate. Meloxicam was exposed directly, and whilst wrapped in aluminium foil, for 7 hours. The finished product packed in one 32 ml and one 100 ml bottle intended for marketing was exposed for 2.8 and 7 hours.

For the solution for injection, no significant change was observed in any of the batches in any containers exposed to light for up to 15 hours.

For the oral suspension, all results were within the specified limits. Based on the obtained results from the long-term, from the accelerated study and from the photostability study the applicant has proposed a shelf-life of 36 months for the oral suspension without any special precautions for storage and 36 months for the solution for injection.

In-use Stability Tests

For the oral suspension an in-use stability study was performed. One batch was taken after the release test and one other batch was taken after being stored 3 months 40°C, 75 % RH. Parameters studied are appearance, relative density, pH, related substances, assay of meloxicam and assay of sodium benzoate. Microbiological contamination and challenge test are performed at the end of stability study. The pack size used 100 ml bottles. The bottles are stored at 25°C, 60 % RH and tested initially, after 1 month, 3 months and 6 months. At each time 5 ml is withdrawn (1 ml per day during 5 days) to simulate in-use conditions. Approximately 25 ml is used each time for analysis.

Three months data were available and results from both batches comply with the specifications. The presented data show no degradation trends and the presented results support the proposed in-use shelf-life. An in-use shelf-life of 6 months without any special precautions for storage was considered acceptable.

For the solution for injection all batches used for stability studies were also subjected to in-use stability testing. Results which were presented indicated that none of the parameters tested changed significantly during the 18 day test period. An in-use shelf-life of 28 days was considered acceptable.

3. SAFETY ASSESSMENT

Oral suspension
The application for MELOXIDYL 1.5 mg/ml oral suspension for dogs is presented in accordance with Article 13.1 of Directive 2001/82/EC as amended. In accordance with this provision, the Applicant will not have to provide the results of toxicological, pharmacological tests and clinical trials if bioequivalence to an authorised product is demonstrated.

Solution for injection
For the extension application for the 5mg/ml solution for injection for dogs and cats, as the reference product has the same pharmaceutical form and the same qualitative and quantitative composition in terms of the active substance, the results of toxicological and pharmacological tests and clinical trials were not required, in accordance with Article 13.1 of Directive 2001/82/EC.

Pharmacological Studies

See below.

Toxicological studies

For the oral suspension, target animal and user safety warnings are the same as those for the reference product. No impact on the environment is anticipated.
For the solution for injection, as the 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.

Pharmacodynamics
For the solution for injection, no data were presented, in accordance with the provisions of Article 13.1 of Directive 2001/82/EC.

User Safety

Inherent Toxicity

As MELOXIDYL 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 NSAIDs 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 has provided a Phase 1 assessment according to the VICH Guideline (CVMP/VICH/592/98). According to the decision tree, the assessment stops at the question 'Will the VMP be used only in non-food animals'. Therefore no further assessment is required.

The disposal advice proposed is the same as 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

Oral suspension

Pharmacokinetics

For the oral suspension the pharmacokinetics were studied during the bioequivalence study following a single oral administration to dogs.

Solution for injection

For the solution for injection adequate assurance of similarity of composition was provided. Exemption 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.

Study design

The bioequivalence study was performed in adult male beagle dogs. The study was a standard two treatment cross-over single dose study comparing the test C531.0 versus the reference Metacam. The animals were randomised to either treatment. The duration of treatment in each period was one day.

Meloxicam is completely absorbed following oral administration. 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. Data from humans on meloxicam show linear kinetics within the dose range 7.5-30 mg and also after multiple doses.

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. Meloxicam undergoes enterohepatic cycling.

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.

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

Test and reference products

Test
C531.0. 150 mg of meloxicam per 100 ml of suspension. Batch number: C531.0/2/P02. Expiry date December 2005.

Adult male beagle dogs with a mean weight of 9.01±0.54 kg at the first period and 8.88±0.55 kg at the second period. Their age was 10.42±0.19 months. The animals were obtained from a recognized centre.

Meloxicam was determined in plasma with an HPLC method with MS/MS detection at CEVA SA, La Ballastière, Libourne, Cedex France. The within study analytical phase began on the 30th of June and finished on the 28th of July 2005.

Sample pre-treatment involved liquid-liquid extraction. Piroxicam was used as internal standard (IS). Specificity was shown employing six independent sources of plasma. No significant interference at the retention times for meloxicam or IS was observed. Sensitivity at the limit of quantification,10 µg/ml, was shown. Satisfactory between- and within-run accuracy and precision was shown for low, medium and high QC sample concentrations. Linearity was demonstrated within the calibration range 10-2000 µg/ml. The recovery was reproducible. Dilution integrity was demonstrated for a dilution factor of 20. Stability in plasma was demonstrated for 4 h at room temperature and over three freeze-thaw cycles. Satisfactory method performance during study sample analysis was demonstrated. Appropriate batch acceptance criteria were used. Repeated analysis was not performed.

The storage period in the study was approximately one month. A tendency to degradation was clearly visible after 5.8 months with 25 % of the samples (2/8) falling outside the acceptance limit of 20 %. However, from the stability tested at two concentrations (20 and 1700 µg/L) acceptable stability was shown (the highest deviation was approximately 7 % from the theoretical concentration).

The parameters analysed were C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, k and CL/F.

Statistical methods

The number of dogs was stated to be sufficient to have 80 to 90 % power to be able to conclude bioequivalence. Pharmacokinetic analysis was performed with KINETICA ver. 4.3 to carry out noncompartmental analysis. ANOVA was used to analyse sequence, period, subject within sequence and treatment. Limits of bioequivalence of the 90 % confidence intervals for the ratio of the point estimates were 0.70-1.43 for Cmax and 0.80-1.25 for AUC_{0-t} and $AUC_{0-\infty}$.

The test and the reference product (Treatment A and B respectively) were compared by ANOVA and 90 % confidence interval. Analysis was carried out on the parameters Cmax/dose and Tmax for the first absorption peak, but the results for the parameters Cmax/dose, Tmax for the second distribution peak, AUCtot/dose and AUClast/dose were also presented. Results are summarised in the following table:

PARAMETERS	TEST ITEM (C531.0) (mean ± SD)	REFERENCE ITEM (METACAM®) (mean ± SD)	RATIO (% ref)	STATISTICAL ANALYSIS Theoretical range	CI 90% %
First peak					
Cmax/dose (µg/L)/µg	0.309 ± 0.035	0.320 ± 0.023	96.25	0.80-1.25	91.47 –101.10 (BE)
Tmax (h)	3.7 ± 0.7	3.5 ± 1.0	-	≤ 0.7 (20%)	0.2 (BE)
Second peak					
Cmax/dose (µg/L)/µg	0.313 ± 0.037	0.320 ± 0.037	97.82	0.80-1.25	94.69 - 101.07 (BE)
Tmax (h)	20.4 ± 5.3	18.3 ± 6.4	-	≤ 3.66 (20%)	2.1 (BE)
AUClast/D(µg.hr/L)	13.346 ± 1.704	13.746 ± 1.694	97.05	0.80-1.25	93.85 – 100.37 (BE)
AUCtot/D (µg.hr/L)	14.120 ± 2.041	14.584 ± 1.964	96.74	0.80-1.25	93.37 – 100.25 (BE)

Theoretical confidence interval:
- the limits of bioequivalence for the ratio of the population mean (Test/Reference) is 0.80 - 1.25.
- the limits of bioequivalence for Tmax, is expressed in percentage of absolute differences (*i.e.* ([Test – Reference] *100/ Reference) ≤20%.).
CI : confidence interval

According to the results, in terms of all parameters C531.0 is equivalent to Metacam.

Study procedures

The study drug was administered as 0.2 mg of meloxicam per kg bodyweight, which corresponds to a dose of 1.33 ml per animal. The animals were administered test and reference products in feed following an overnight fast. The animals were housed in individual stainless cages and during the wash-out phase in another place. Acclimatisation lasted 7 days before start of treatment. Blood samples were collected pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, 24, 30, 36, 48, 60, 72 and 96 hours after administration. Wash-out lasted for 14 days.

Blood sampling is considered sufficient to cover the absorption phase more than enough and the enterohepatic cycling and also to have a proper estimate of the AUC, both AUC_{0-t} and $AUC_{0-\infty}$ and T_{max} and C_{max}. Since meloxicam shows linear kinetics both after single and multiple doses, the single dose study design is appropriate to establish bioequivalence.
Results

Treatment	**AUC_{0-t}** µg x L/h	**$AUC_{0-\infty}$** µg x L/h	**$AUC_{tot/Dose}$** µg x L/h	**C_{max}** µg/ml	**t_{max}** h	**$T_{1/2}$** h
Test	24226±4027	25647±4697	14.120±2.041	590.24±64.78	10.5 (3-24)	21.47±2.799
Reference	25134±3822	26674±4324	14.584±1.964	613.67±65.60	7.5 (2-24)	21.94±2.758
***Ratio (90% CI)**	(0.93-1.00)	0.92-1.00)	0.93-1.00	(0.93-0.99)	-	-

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration
$T_{1/2}$	half-life

**ln-transformed values.*

Some of the dogs experienced diarrhoea the day after administration of the test product in the first phase. This was not seen in any of the dogs following administration of the reference product. This is unlikely to have had an influence on bioavailability.

Gastrointestinal disorders are well known side effects for NSAIDS. However, no explanation in terms of any experimental condition or difference in excipients between test and reference product has been found to explain the adverse effects observed following dosing with test product but not following administration of reference product.

A further study was submitted. In this study, dogs received via oral route either the reference product or test product according to a randomised, two period, two treatment, two sequence crossover design. This study was first carried out to evaluate the bioequivalence between test and reference product following a single oral administration to dogs. In this study the test product was not administered with feed. Each animal received the recommended dose of about 0.2 mg/kg bw of meloxicam for both products.

The in life phase of the trial had the following schedule.

Approximate Trial Day	Event
Between Day –11 and Day 0	Acclimation, observation of animals and allocation of animals
Day 0	Weighing, treatment, sampling and observation of animals
Days 1 to 4	Sampling and observation of animals
Days 5 to 13	Observations of animals
Day 14	Weighing, treatment, sampling and observation of animals
Days 15 to 18	Sampling and observation of animals

A wash-out period of 14 days was maintained between each treatment. Acclimatisation lasted 11 days prior to treatment. Each animal received once daily a ration of about 300g pelleted food during the acclimatisation period. Food was removed at approximately 1 p.m. on the day before each treatment. Food was administered just after treatment. The animals were observed during the duration of the study.

The following results were obtained:

Animal number	ID number	Sequence	Treatment period 1						Treatment period 2				
			D0	D1	D2	D3	D4	D11	D14	D15	D16	D17	D18
1	282363	BA	-	-	-	-	-	-	-	-	-	-	-
2	115192	AB	-	-	-	-	-	-	-	-	-	-	-
3	857953	AB	-	-	-	-	-	V	V	-	-	-	-
4	981556	AB	-	-	-	-	-	-	-	-	-	-	-
5	145787	BA	-	-	-	-	-	-	-	-	-	-	-
6	854998	BA	-	-	-	-	-	-	-	-	-	-	-
7	857332	AB	-	-	-	-	-	-	-	-	-	-	-
8	771173	BA	-	-	-	-	-	-	-	-	-	-	-
9	117237	AB	-	-	-	-	-	-	-	-	-	-	-
10	926046	AB	-	-	-	-	-	-	-	-	-	-	-
11	976062	BA	-	-	-	-	-	-	-	-	-	-	-
12	975220	BA	-	-	-	-	-	V	-	-	-	-	-
13	972206	BA	-	-	-	-	-	-	-	-	-	-	-
14	872630	AB	-	-	-	-	-	-	-	-	-	-	-
15	936606	AB	-	-	-	-	-	-	-	-	-	-	-
16	958396	BA	-	-	-	-	-	-	-	-	-	-	-

D0: day of treatment for the first period
D14: day of treatment for the second period

Only 3 cases of vomiting (undigested pelleted feed) were observed for the 2 periods; two cases at day 11(following administration at D0 of test product for one animal, and reference product for the other) and one case at D14 at 1:30 pm (following administration at D14 8:26 am for the reference product). No other clinical signs were observed during the study. The results observed in this study allowed concluding that the same incidence of vomiting is observed following administration of the test and the reference product. No cases of diarrhoea were observed following the administration of either product. Furthermore, it seems that no difference in excipients between the test and the reference product could explain the adverse effects observed in the firstly submitted bioequivalence study.

The test substance used in the two studies is of the same batch (C531.0/2/P02). The design of this study differs in terms of feeding state at administration. Fasted animals would be more likely to present GI-related adverse reactions following oral administration of NSAIDs. This would therefore indicate a theoretical excipient – meloxicam-interaction to be unlikely. Considering that the observed reactions in the firstly submitted trial was only observed in the first, not second, phase of that trial without any change of experimental conditions, this issue need not be further addressed. GI-related adverse reactions will be reported and discussed in the PSURs.

The safety profile 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. MELOXIDYL 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 BALANCE

Oral suspension
The application for MELOXIDYL 1.5 mg/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 1.5 mg/ml oral suspension for dogs.

The composition is mainly based on the composition of the reference product. The active substance meloxicam is manufactured by two manufacturers both of whom have submitted complete ASMFs together with valid letters of access.

This application is made in accordance with Article 13.1 of Directive 2001/82/EC as amended. No toxicological data have been submitted, and are not required as bioequivalence to the reference product is demonstrated.

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

1. bioequivalence between the two products;
2. a satisfactory impurity profile of meloxicam in MELOXIDYL;
3. the fact that a comparable safety profile was obtained with both products in the bioequivalence study.

GI-related adverse reactions will be reported and discussed in the PSURs. 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:

1. People with known hypersensitivity to NSAIDs should avoid contact with the veterinary medicinal product

2. In case of accidental ingestion, seek medical advice immediately and show the package insert or the label to the physician.

MELOXIDYL 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. A bioequivalence study was performed as a standard two treatment cross-over single dose study comparing the test substance versus the reference Metacam. A further study was submitted and the design of this study differed in terms of feeding state at administration. 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.

Solution for injection
The 5 mg/ml solution for injection has been formulated to be pharmaceutically equivalent to Metacam solution for injection. It contains the same active substance (meloxicam) and the same preservative (ethanol anhydrous) in the same concentrations as the originator product.

The relevant risks associated with this product are covered in the product information which is in line with the reference product.

The product does not contain any material of animal origin and no material of animal origin is used during the manufacturing process.

Based on the data provided, it was accepted that the product has an acceptable safety profile in the target species when administered at the recommended treatment. Target animal and user safety warnings are the same as those for the reference product.

An environmental risk assessment stopped in Phase I. As the product is clearly intended for use in individual companion animals, exposure of the environment is likely to be low and no further information was considered necessary.

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.
-"Accidental self-injection may give rise to pain" is included for 5 mg/ml solution for injection presentation.

MELOXIDYL 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. Based on information provided, MELOXIDYL 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 will be the same as the reference product.

The indications and posology as authorised for the reference product can be applied to MELOXIDYL 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 overall benfit- risk evaluation was deemed positive with a sufficiently clear and complete SPC and product literature.

Based on the original and supplementary data presented, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of MELOXIDYL were considered to be in accordance with the requirements of Directive 2001/82/EC as amended.

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MELOXIDYL 20 MG/ML SOLUTION FOR INJECTION FOR CATTLE, PIGS AND HORSES

INTRODUCTION

An application for an extension of a Community marketing authorisation of MELOXIDYL 20 mg/ml, solution for injection for cattle, pigs and horses has been submitted to the EMEA on March 3rd 2009 by Ceva Santé Animale in accordance with Article 2(a) of Commission Regulation (EC) No 1085/2003 and Annex II point 2 and indent (iv) thereof.

MELOXIDYL 20 mg/ml solution for injection contains meloxicam, and is presented in packs/containers of 50, 100 and 250 ml.

It is indicated for use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle, for use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle and for adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy in cattle.

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

It is indicated for use in the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders and for the relief of pain associated with equine colic in horses. The route of administration is subcutaneous, intramuscular and intravenous. The target species are cattle, pigs and horses.

PART 1 - ADMINISTRATIVE PARTICULARS

Pharmacovigilance system

The Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

GMP

During the assessment of the chemical and pharmaceutical documentation no issues have been identified which would trigger an inspection of any of the manufacturing sites of this marketing authorisation application.

PART 2 - QUALITY

Composition

The finished product MELOXIDYL 20 mg/ml solution for injection for cattle, pigs and horses is a sterile, clear to yellowish solution containing meloxicam as active ingredient. The meloxicam solution is intended for multiple use and contains ethanol as antimicrobial preservative. The formulation also contains meglumine as an alkalising agent, macrogol 300 and poloxamer 188 as solubilisers, glycine as buffering agent, disodium edetate as stabilising agent, sodium hydroxide and hydrochloric acid as pH adjusters, and water for injections as solvent.

Container

MELOXIDYL 20 mg/ml solution for injection is packaged in 50, 100 or 250 ml colourless type I glass vials which are closed with bromobutyl rubber stoppers and aluminium caps.

Development Pharmaceutics

The product has been formulated to be pharmaceutically equivalent to the reference product, Metacam 20 mg/ml solution for injection for cattle, pigs and horses (marketed by Boehringer Ingelheim) and is stated to be of identical composition, qualitatively and quantitatively, as the reference product.

Method of manufacture

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

The process has been satisfactorily validated for pilot batches manufactured by BIOVE, a subcontract manufacturer which was in charge of the pilot batches manufacture. Process validation data for one industrial batch produced by the proposed finished product manufacturer, Ceva Sante Animale, has been given, and the applicant commits to perform a full validation study on the next two industrial batches.

The applicant has informed that the proposed formulation will not be marketed and that a change in the formulation will be applied (by a variation) prior to marketing. The change in formulation cannot be applied during the present procedure. In light of the change in formulation proposed by the applicant, the applicant has provided a commitment not to market the product until the change in formulation has been approved through a variation procedure.

Control of starting materials

Active substance
The active ingredient, meloxicam, has a monograph in the European Pharmacopoeia (Ph. Eur.) The information presented in the ASMF is considered sufficient to support the application for the drug product.

Meloxicam is controlled by the applicant according to the Ph. Eur. monograph (no. 2373) current edition. Moreover, a test for residual solvents is added. The specification is considered acceptable, as the applicant has justified the omission of a test for microbiological quality in the specification by including an in-process test for bioburden of the drug product.

Stability data for three batches of meloxicam covering 24 months at 30°C/65% RH and 6 months at 40°C/75% RH has been provided and the data support a re-test period of 2 years.

Excipients
The following excipients are used in the formulation: ethanol as antimicrobial preservative, meglumine as an alkalising agent, macrogol 300 and poloxamer 188 as solubilisers, glycine as buffering agent, disodium edetate as stabilising agent, sodium hydroxide and hydrochloric acid as pH adjusters, and water for injections as solvent. All excipients comply with their respective Ph. Eur. monographs. The applicant has justified the omission of a test for microbiological quality of the excipients by including an in-process test for bioburden of the drug product.

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

It is stated that none of the ingredients in MELOXIDYL 20 mg/ml solution for injection are of animal origin.

Control tests during production

During manufacture, adequate process controls are applied.

Control tests on the finished product

The proposed release specifications are generally considered justified and supported by the batch analysis data provided. Tests are included for appearance of packaging and product, clarity, degree of coloration, content, density, pH, identification of meloxicam, assay of meloxicam and ethanol, purity test and sterility. The impurity limits are in compliance with the VICH GL 11 guideline on impurities in new veterinary medicinal products and are thus acceptable. The identity of the active substance is acceptably verified by two independent methods, retention time by HPLC and UV spectrophotometry. The content of the preservative ethanol is determined by gas chromatography and the limits proposed at release are considered acceptable. Some issues that were raised on e.g. the validation of the purity HPLC method and the content of ethanol method have been resolved. Moreover, efficacy of antimicrobial preservation has been demonstrated at the proposed lower shelf-life limit.

Regarding the proposed shelf-life specifications for the finished product, the applicant has tightened the lower shelf-life limit of pH and the shelf-life limit for the content test. Furthermore, the shelf-life limits for ethanol content are justified.

Stability

A stability study on pilot scale is ongoing. Three bulk solution batches filled into three different filling volumes gives nine product batches. The stability study programme design, which is a combination of bracketing and matrixing, is considered acceptable. A 28 days in-use study has been presented and, in addition, a photo-stability study and a freeze-thaw study have been performed on the drug product.

Stability data are provided covering 18 months for samples stored at long-term (25°C/60% RH) and 6 months at accelerated conditions (40°C/75% RH), in the package proposed for marketing. All results presented comply with the proposed stability specifications. No obvious trends are seen, except for a change in degree of coloration from Y3 to Y1-Y2 (still within the proposed shelf-life specification limits). For ethanol content there are some fluctuations in the results, but no trend is seen. No difference is seen in the results between samples stored in inverted and upright position. All impurities results are below the reporting limit (0.3%). Based on the stability data provided, a shelf-life of 30 months with no special restrictions of storage is considered acceptable.

An in-use time of 28 days is considered acceptable based on the in-use stability data provided. Additional data is required only if future deviations are found. Based on the photostability study results the product is considered photostable.

Moreover, for the container-closure interaction study, which is ongoing, results after 12 months storage are given and judged as acceptable.

Overall conclusions on quality

All issues raised on the quality part have been resolved. From a quality point of view the product is now approvable. The applicant has provided a commitment not to market the product until the change in formulation has been approved through a variation procedure.

PART 3 – SAFETY

Since this product has an identical qualitative and quantitative composition as the originator, a bioequivalence study with a suitable reference product does not need to be provided. The results of toxicological and pharmacological tests and clinical trials are not required, in accordance with Article 13.1 of Council Directive 2001/82/EC as amended.

User safety

An acceptable justification for not submitting an assessment of user safety has been submitted.
The proposed user warnings are in accordance with the originator´s warnings and are therefore considered acceptable.

Environmental risk assessment

A detailed Environmental Risk Assessment in accordance with current VICH and CVMP guidelines was provided. The assessment ended with PECsoil calculations for pigs, cattle, and horses as intensively reared, as well as for cattle and horses as pasture animals. All calculated PECsoil values were below the trigger value of 100 µg/kg and the assessment stopped in Phase I.

Overall conclusions on the safety documentation

It is acceptable to use the same user warnings as for the originator since the reference product has the same pharmaceutical form and the same qualitative and quantitative composition.

It can be concluded that the use of MELOXIDYL 20 mg/ml solution for injection for cattle, pigs and horses, in accordance with the SPC, is not likely to result in an unacceptable risk to the environment.

Residues documentation

The applicant has provided a justification for not submitting a tissue residue study:

1. The generic has the same qualitative and quantitative composition as the reference product
2. The dose schedule and route of administration in each species (cattle, pigs and horses) is the same
3. The target species are the same

Hence, the withdrawal periods of the reference product can be used without further justification

Overall conclusions on the residues documentation

It is acceptable to use the same withdrawal periods as for the originator, since this is a generic application for a product with identical qualitative and quantitative documentation.

PART 4 – EFFICACY

Pharmacokinetics

No new information has been provided and none is needed. The identical composition and the fact that this product is intended for injection, is acceptable to waive an *in vivo* bioequivalence study.

Pharmacodynamics, Efficacy and Safety

The pharmacodynamic properties of meloxicam have been evaluated in laboratory species, cattle and dogs. Meloxicam is an NSAID of the oxicam class with anti-inflammatory, analgesic and anti-exudative

effects. No new data have been provided and none is needed. Since this is a generic application, efficacy and safety data have not been provided and none is needed.

PART 5 – BENEFIT RISK ASSESSMENT

Introduction

MELOXIDYL, active substance: meloxicam 20 mg/ml
Extension application of a generic product

Benefit assessment

Direct therapeutic benefit
No difference from the originator is expected, based on that the product has an identical qualitative and quantitative composition and is a formulation intended for injection.

Additional benefits

No additional benefits compared to the originator are expected or have been shown as this is a generic application.

Risk assessment

The relevant risks associated with this product are covered in the product information (to be in line with the originator).

Risk management or mitigation measures

The applicant has an acceptable pharmacovigilance system in place.

Evaluation of the benefit risk balance

Since this is a generic product to an injection formulation with identical quantitative and qualitative composition, similar efficacy and safety is expected.

The formulation and manufacture of MELOXIDYL is described and specifications proposed, however some pharmaceutical issues were to be addressed by the applicant. All issues raised on the quality part have now been resolved. The change in formulation should be approved through a variation procedure before marketing of the product.

The tolerance of the target animals is not expected to show any differences compared to the originator. Tolerance, environmental risk and user safety is expected to be in line with the originator. Appropriate warnings in line with the originator are included in the SPC.

Conclusion on benefit risk balance

From an efficacy and safety point of view, the overall benefit risk evaluation is deemed positive since this is a generic product with identical quantitative and qualitative composition as the originator. With a few linguistic changes to the product information, the product is deemed approvable from an efficacy and safety point of view. From a quality point of view the product is now considered approvable.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of MELOXIDYL 20mg/ml solution for injection for cattle, pigs and horses were considered to be in accordance with the requirements of Council Directive 2001/82/EC, as amended, that the benefit-risk balance was favourable and that the application is approvable.

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MELOXIDYL 0.5 MG/ML ORAL SUSPENSION FOR CATS

INTRODUCTION

An application for an extension of a Community marketing authorisation of Meloxidyl has been submitted to the EMEA on 30 July 2009 by Ceva Sante Animale in accordance with Article 2(a) of Commission Regulation (EC) No 1085/2003 and Annex II thereof.
Meloxidyl oral suspension for cats contains meloxicam and is presented in bottles of 15 ml in a cardboard box. It is indicated for the alleviation of inflammation and pain in chronic musculo-skeletal disorders. The route of administration is oral use. The target species is cats.

PART 1 - ADMINISTRATIVE PARTICULARS

The Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

PART 2 - QUALITY

Composition
The finished product Meloxidyl 0.5 mg/ml oral suspension for cats contains meloxicam as active ingredient and sodium benzoate as preservative.

Container
The finished product is packaged in polyethylene bottles with a syringe for sampling of the product.

Development Pharmaceutics
The product has been formulated to be pharmaceutically equivalent to the reference product, Metacam 0.5 mg/ml oral suspension for cats (marketed by Boehringer Ingelheim). The composition of the product has been justified.

Method of manufacture
The finished product is manufactured according to standard procedures. The manufacturing process and the performed in-process controls are specified in a manufacturing process flow chart and the different manufacturing operation steps are described in sufficient detail. The manufacturing process has been adequately validated on production scale batches.

Control of starting materials

Active substance
The active ingredient meloxicam is controlled by the applicant according to the Ph. Eur. monograph. The meloxicam is micronised at the applicant's request by a laboratory specialised in powder micronisation. The proposed re-test period of 5 years without any specific storage conditions for non micronised meloxicam is considered acceptable. For micronised meloxicam the stability data provided support a re-test period of 1 year without any specific storage conditions.

Excipients
All excipients, i.e. xanthan gum, colloidal anhydrous silica, sorbitol liquid (non-crystallising), glycerol, xylitol, sodium benzoate, citric acid anhydrous and purified water, are described in Ph. Eur. and are tested in accordance with the current Ph. Eur. monographs.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Meloxidyl 0.5 mg/ml oral suspension complies with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01).

Control tests on the finished product
The description of the methods used for the control of the finished product and the specifications are provided. The product is tested according to generally acceptable specifications, the additional information requested has now been provided.

Stability
The real-time stability studies are ongoing and will be followed up to 48 months. Updated stability data covering 18 months has now been provided (formerly 9 months). The in-use stability study has now been completed and 6 months data is provided (formerly 3 months). The proposed in-use shelf-life of 6 months is accepted. A shelf-life of 30 months (by extrapolation, 18+12 months) with no special precautions for storage is currently considered acceptable for the product as packaged for sales.

Overall conclusions on quality
The application is recommended for approval now that complementary information have been received and judged to be acceptable.

PART 3 – SAFETY

Pharmacodynamics

Please see section 4, Efficacy, Pharmacodynamics.

Pharmacokinetics

No residue studies were performed. This is acceptable, since this product is not intended for food producing animals. For the pharmacokinetic bioequivalence study performed in cats, see section 4.

No pharmacokinetic data other than the bioequivalence study has been provided.

Toxicological studies

No data have been presented since this application is made in accordance with Article 13 of Directive 2001/82/EC as amended. For such applications it is acceptable not to provide the results of toxicological studies.

Studies of other effects

No data have been presented since this application is made in accordance with Article 13 of Directive 2001/82/EC as amended. For such applications this is considered acceptable.

User safety

A discussion on user safety has been provided for this generic product. No specific user safety study has been performed. The impact of the active ingredient, meloxicam is expected to be the same as for the originator, since bioequivalence was shown. The applicant claims that the excipients do not constitute a hazard to the user, saying that they are of well established use in oral formulations.

The following excipients are included: citric acid, anhydrous, glycerol, silica, colloidal anhydrous, sodium benzoate, sorbitol, liquid, xanthan gum, xylitol and water. The product information states a warning for people with hypersensitivity to the preservatives. The same warnings as for the originator apply to this product.

Environmental risk assessment

The applicant has provided a Phase 1 assessment according to the VICH Guideline (CVMP/VICH/592/98). According to the decision tree, the assessment stops at the question 'Will the VMP be used only in non-food animals'. Therefore no further assessment is required. Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

Overall conclusions on the safety documentation

No data other than a discussion on the ERA and user safety have been presented since this application

is made in accordance with Article 13 of Directive 2001/82/EC as amended. This is considered acceptable.

Residues documentation

Not applicable.

PART 4 – EFFICACY

A two-way cross-over study in 18 male cats was performed, comparing the rate and extent of absorption from Meloxidyl 0.5 mg/ml, oral suspension with Metacam 0.5 mg/ml. The study was performed at Avogadro, Fontenilles, France, and the analytical phase by the Bioanalytical Laboratory of Preclinical development Department of CEVA Santé Animale, La Ballastière, Libourne, Cedex, France. It is stated that the study has been performed in accordance with GLP and Directive 2004/10/EC.

A dose of 0.1 mg/kg was administered of each formulation. A wash-out period of 2 weeks was applied, considered sufficient given the elimination half-life of meloxicam of 24 hours. Blood for the analysis of meloxicam was sampled pre-dose and up to 96 hours. A LC-MS-MS method was used as analysis method. Non-compartmental analysis was performed to obtain the pharmacokinetic data. The pharmacokinetic parameters determined (in WinNonlin version 5.2) were Cmax, tmax, AUC_{0-t}, $AUC_{0-\infty}$, C_{max}/Dose and $AUC_{0-\infty}$ /Dose. The results show that all pharmacokinetic parameters fulfil the criterion of 90 % confidence intervals of the geometric means of 0.8-1.25. The two major objections raised based on that basal important information of the bioanalysis method were missing is now considered solved. Long-term stability data (corresponding to the time samples were stored in the study or longer) was shown and the results of the quality control samples from the within study bioanalysis shows satisfactory performance.

Pharmacodynamics

Meloxicam is an NSAID of the oxicam class with anti-inflammatory, analgesic and anti-exudative effects. Since this is an extension application of a generic, efficacy and safety data have not been provided and none are needed.

Target animal tolerance and user safety are expected to be the same as for the originator. The product information should be in line with the originator.

Palatability

In a palatability study cats received a single oral dose of 0.05 mg meloxicam per kg body weight in the form of Metacam 0.5 mg/ml or Meloxidyl 0.5 mg/ml oral suspensions deposed on pelletised food. The study demonstrates that most of the cats accepted both items within one hour after food distribution.

Overall conclusion on efficacy

Meloxicam is an NSAID of the oxicam class with anti-inflammatory, analgesic and anti-exudative effects. Since this is an extension of a generic application, efficacy and safety data have not been provided and none are needed.

Palatability of Meloxidyl 0.5 mg/ml oral suspension with pelletised food was demonstrated.

PART 5 – BENEFIT RISK ASSESSMENT

Introduction
Meloxidyl, active substance: meloxicam 0.5 mg/ml
Extension application of a generic product

Benefit assessment

Direct therapeutic benefit
No difference from the originator is expected, based on that the product has an identical qualitative and quantitative composition and is a formulation intended for injection.

Additional benefits
No additional benefits compared to the originator are expected or have been shown as this is a generic application.

Risk assessment
The relevant risks associated with this product are covered in the product information (to be in line with the originator).

Risk management or mitigation measures
The applicant has an acceptable pharmacovigilance system in place.

Evaluation of the benefit risk balance
Since this is an extension of a generic product to an oral suspension formulation, being comparable in terms of active substance, similar efficacy and safety is expected. The excipients included in the product are well known and widely used and described in Ph. Eur. A satisfactory impurity profile of meloxicam in Meloxidyl has been established.

The formulation and manufacture of Meloxidyl is described and specifications proposed, however some pharmaceutical issues need to be addressed by the applicant.

From the assessment of the bioequivalence study, two major objections arose with respect to the bioanalytical method, long-term stability data of samples (corresponding to the time period samples were stored or longer) and the results of QC-samples within the study.

The tolerance of the target animals is not expected to show any differences compared to the originator. Tolerance, environmental risk and user safety are expected to be in line with the originator. Appropriate warnings in line with the originator are included in the SPC.

Palatability of Meloxidyl 0.5 mg/ml oral suspension was demonstrated.

Conclusion on benefit risk balance
The two major objections regarding the bioanalytical method used in the bioequivalence study are now considered solved. The outstanding issues regarding the quality part have now been addressed and are resolved.

The product information is expected to be revised in the light of the answers to questions from CVMP.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the application for Meloxidyl 0.5 mg/ml oral suspension in cats is approvable.