EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines and Product Data Management

Scientific discussion

This module reflects the initial scientific discussion for the approval of Melosus (as published in February 2011). For information on changes after this date please refer to module 8 of the EPAR (Steps taken after authorisation).

1. Summary of the dossier

Melosus 1.5 mg/ml oral suspension for dogs and 0.5 mg/ml oral suspension for cats are intended for the alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders in dogs and the alleviation of inflammation and pain in chronic musculo-skeletal disorders in cats. Melosus was eligible for assessment by the centralised procedure under article 3.3 of Regulation (EC) No 726/2004.

The active substance of Melosus is meloxicam, a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class, ATCvet code: QM01AC06, which acts by inhibition of prostaglandin synthesis, thereby exerting anti-inflammatory, analgesic, anti-exudative and antipyretic effects. It reduces leukocyte infiltration into the inflamed tissue. To a minor extent it also inhibits collagen-induced thrombocyte aggregation.

The benefits of Melosus are the alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders in dogs and the alleviation of inflammation and pain in chronic musculo-skeletal disorders in cats. Typical adverse reactions of NSAIDs such as loss of appetite, vomiting, diarrhoea, faecal occult blood and apathy have occasionally been reported. These adverse reactions 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.

The approved indication is: "alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders in dogs and the alleviation of inflammation and pain in chronic musculo-skeletal disorders in cats."

2. Quality assessment

Composition

The product is presented in two strengths: 0.5 mg/ml and 1.5 mg/ml. The basic formulation is the same for both, except for the active substance content.

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The 0.5 mg/ml is presented in 25 ml HDPE bottles and the 1.5 mg/ml in 25 ml, 50 ml and 125 ml HDPE bottles. Acceptable details of the packaging and the dosing syringes were given. Dose accuracy and precision meet European Pharmacopoeia (Ph. Eur.) requirements.

Clinical Trial Formulae

Two bioequivalence studies were performed, one with a batch of the 0.5 mg/ml product strength and one with a batch of the 1.5 mg/ml product strength. Both had the same formulation as that proposed for marketing. The test products were manufactured according to the method described by the finished product manufacturer. The reference products used in the bioequivalence studies were Metacam 0.5 mg/ml oral suspension and Metacam 1.5 mg/ml oral suspension (marketing authorisation holder Boehringer Ingelheim Vetmedica).

Development Pharmaceutics

A brief account of the development of the product was given. Overall, the product is appropriately formulated. The excipients are commonly used in medicinal products and or food products and the role of each in the formulation is described.

The products have been formulated to be essentially similar to the reference products Metacam 0.5 mg/ml and 1.5 mg/ml oral suspension. The products contain meloxicam at a concentration of 0.5 mg/ml or 1.5 mg/ml and are presented as oral suspensions. Bioequivalence between the 0.5 mg/ml and 1.5 mg/ml strengths and the reference products is discussed in the Efficacy Section of this document. The packaging components are of a type commonly used for pharmaceutical products. Opaque containers are justified due to the known light sensitivity of meloxicam. A discussion of the residual solvents status of the products was provided. Residues have been shown to comply with the guideline VICH GL18: Impurities: Residual solvents (CVMP/VICH/502/99).

Method of Preparation

Manufacturing Formula and Batch Size

Manufacturing formulae for the proposed batch size were provided. The manufacturing formulae are correctly derived from the unit formulae.

Manufacturing Process and In-process Controls

An outline flow chart and brief narrative of the process were provided. The applicable in-process controls were described.

Control of Starting Materials

Active Substance

Specification and routine tests

Active ingredients listed in a Pharmacopoeia.

Meloxicam

A Drug Master File (DMF) for the active substance manufacturer was provided. The EDMF was in the CTD format and made reference to the monograph published in the British Pharmacopoeia (BP). In addition to the BP monograph, a monograph for meloxicam is included in the Ph. Eur. Version 6.3 and

is effective from 1 January 2009. An updated EDMF, taking into account the existence of the Ph. Eur. monograph and demonstrating compliance, was supplied during the procedure, including both the applicant's part and the restricted part.

Analytical methods and validation

Assay of meloxicam is by non-aqueous titration and related substances are determined by the methods described in the Ph. Eur. monograph and are therefore considered validated. Other relevant test methods described are those of the Ph. Eur. monograph. The in-house methods used for particle size and the residual solvents have been validated.

Active ingredients not listed in a Pharmacopoeia.

Not applicable.

Physico-Chemical Characteristics liable to affect bioavailability

Meloxicam exists in five polymorphic forms I - V. These forms can be differentiated on the basis of their infrared absorption spectra and X-Ray diffraction patterns. The active substance manufacturer routinely manufactures polymorphic form I.

Particle size is limited on the active substance specification.

Scientific data

Nomenclature

International Non-proprietary Name (INN) Meloxicam

IUPAC Name	4-hydroxy-2-methyl-N-(5-methyl-1,3-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1-1-dioxide
Molecular Formula	$C_{14}H_{13}N_3O_4S_2$
Molecular Weight	351.41
Appearance	Pale yellow coloured powder
Pharmaceutical form:	Oral suspension

Development Chemistry

The structure has been shown analytically. Satisfactory data were provided. The route of synthesis also confirms the structure of meloxicam.

Physico-chemical characterisation

The solubility is described in the Ph. Eur. monograph. No literature describes isomerism for meloxicam.

Impurities

The applicant has identified a number of potential impurities in meloxicam. It was concluded that the monograph methods are suitable to control potential impurities.

Solvents used in the process are limited on the specification in line with VICH guidelines. Data were presented for a number of production batches demonstrating that levels of these solvents are less than 10% of the VICH limit. The analytical method used has been fully validated.

Batch analysis

Batch data demonstrating compliance with the specification as given in the EDMF were provided for a number of batches.

Excipients

Specifications and routine tests

Excipients described in a Pharmacopoeia

Satisfactory certificates of analysis were provided.

Excipient not described in a Pharmacopoeia

Anise aroma.

Scientific data

No further information is required for the excipients described in a pharmacopoeia. Concerning anise aroma the supplier's data confirm that this flavour meets the requirements of Council Directive 88/388/EEC on food flavourings.

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

A declaration that the excipients and active ingredient are not of animal origin and that no materials of animal origin are used in the process was provided in accordance with guidance "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 intermediate products

Not applicable. There are no intermediate products.

Control tests on finished product

Product Specification and Routine Tests:

The finished product release specification is identical for both product strengths (active substance and preservative limits being expressed as % nominal). The specification is considered suitable for the dosage form and the testing methods have been described in sufficient detail.

Scientific Data:

The analytical methods used for the finished product have been adequately validated. Batch data demonstrating compliance with the specification were provided for a number of batches.

Stability

Stability Tests on the Active Substance(s)

Batches have been subjected to stability testing using the methods of the active substance specification. Polymorphic form and particle size have also been determined. No significant change was recorded after 5 years storage at 25°C/ 60% relative humidity (RH), 6 to 12 months storage at 25°C/ 60% RH or 6 months storage at 40°C/ 75% RH.

Stability Tests on the Finished Product

Specification

The specification for shelf life and analytical methods were described.

Stability Tests

A stability study has been initiated on batches of each product strength. A commitment was provided that additional full scale batches of each strength will be placed on stability according to the same protocol. All relevant parameters of the current specification are tested. Samples were additionally tested for particle size. A photostability study under VICH conditions was conducted on batches of 0.5 mg/ml and 1.5 mg/ml strengths. Based on the results provided it is concluded that the product is not sensitive to light and that a warning to protect from light is not required.

In-use Stability Tests

In use stability testing has been conducted on freshly manufactured batches of the 1.5 mg/ml product and 0.5 mg/ml product. Aged batches were also tested. Samples were stored at 25°C/ 60% RH. The study is severe as it involves storage of opened bottles without their caps. Full testing was carried out and no significant deterioration was observed.

Requests for inspection action prior to authorisation:

Not applicable.

OVERALL CONCLUSION ON QUALITY

An account of the development of the product was given. Data on antimicrobial preservative efficacy were satisfactory. The manufacturing process has been adequately described and sufficiently validated. Satisfactory details of the manufacture and control of meloxicam were provided in the form of an EDMF. The specifications and data on the excipients and packaging materials were adequate. The finished product specifications for use at release and throughout the life of the product were adequate and include appropriate tests. Methods have been validated where necessary.

The stability data on the active substance and dosage form support the retest interval of 2 years and the shelf-life as packaged for sale of 3 years respectively. The shelf-life after first opening of the immediate packaging is 6 months.

Overall, quality is considered acceptable.

3. Safety assessment

Safety Testing

As Melosus is a generic of Metacam, and bioequivalence has been demonstrated (see Efficacy Section), safety data were not required.

Pharmacological Studies

Pharmacodynamics

As this is an application for a generic product, there are no requirements for pharmacodynamics data. Nevertheless the pharmacodynamics of meloxicam were addressed in the dossier.

Pharmacokinetics

The results of bioequivalence studies are discussed in the Efficacy Section of this report.

Toxicological studies

The applicant has claimed exemption to provide any safety studies. In the dossier an extensive evaluation of the pharmacology and toxicology of meloxicam was provided.

The applicant has claimed bioequivalence with Metacam 1.5mg/ml oral solution and that data in support of the pharmacology and toxicology of meloxicam are not required. The results of the studies provided (see Efficacy Section) support the bioequivalence of the two products. In terms of the pharmacology and toxicology of meloxicam the claim of bioequivalence is accepted (see Efficacy Section).

User Safety

A user risk assessment in support of the potential exposure of the user to the product was provided which is considered acceptable and supports the proposed user safety warnings in the SPC and product literature. User safety is considered to be addressed satisfactorily.

The applicant has included the following user safety warnings in the SPC and product literature:

"*People with known hypersensitivity to 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*."

The user safety warnings are considered appropriate for a product of this type.

Environmental risk assessment

The applicant has provided an environmental risk assessment in compliance with VICH GL6 (Environmental impact assessment for veterinary medicinal products – Phase I). As the product is indicated for non-food animals and the active substance is an NSAID, which will limit the use of the product to small numbers of animals, environmental exposure will not be extensive. The environmental risk assessment can end at Phase I. The use of Melosus is not expected to pose a risk for the environment.

Residue documentation

Not applicable, since the product is for administration to companion animals only.

CONCLUSION

A satisfactory user risk assessment was provided, addressing all potential routes of exposure of the user to the product. Appropriate warnings for use are provided. The use of Melosus is not expected to pose a risk for the environment when used in accordance with the SPC. The application is considered acceptable as regards human and environmental safety issues.

4. Efficacy assessment

Preclinical Studies

Pharmacology

Pharmacodynamics

The application was made in accordance with article 13(1) of Directive 2001/82/EC, as amended, for a generic product, and therefore data on pharmacodynamics are not required. However, the clinical expert's critical summary has made a review of the scientific literature relevant to pharmacodynamics.

Pharmacokinetics

The applicant has presented two bioequivalence studies in support of this application.

Dogs

A bioequivalence study was performed comparing two meloxicam oral suspensions formulations at a dose of 0.2 mg/kg bodyweight (bw) administered orally to healthy dogs. It was a GLP compliant two-period, two-sequence crossover study with a wash out period of 14 days. The study was block randomised. The objective was to assess bioequivalence between the test item (TI) and the reference item (RI) both containing 1.5 mg/ml of meloxicam in beagle dogs after a single oral dose of 0.2 mg meloxicam per kg bw of suspension. The test article was meloxicam (1.5 mg meloxicam/ml) 1.5 mg/ml oral suspension; batch of proposed commercial formulation. A certificate of analysis was provided. The reference article was Metacam (1.5 mg meloxicam/ml) oral suspension; batch of an existing commercial formulation with a certificate of analysis provided.

Healthy male and female Beagle dogs were randomised into 2 groups according to sex and bw and also taking into account their non-relationship. There was an acclimatisation period and each treatment period consisted of a single treatment day (a dose of 0.2 mg meloxicam/kg bw), and a further follow-up period in which blood samples were taken. The dose was justified as being the standard dose which is safe and provides adequate plasma concentrations. The test item was administered as a one-off dose into the mouth by syringe. It was checked if the dog had swallowed the dose and then drinking water was administered by probing. During the study, all animals were examined daily from day -7 till day -1 and twice daily from day 0 till day +20 to evaluate their general health status. Blood samples for the determination of meloxicam concentration in plasma were collected at various times before treatment and after the administration in each treatment phase. All plasma samples were stored until they were transported for analysis.

This study was well designed and conducted. Dogs were appropriate subjects as they are the proposed target species. The number of dogs was adequate. Plasma sampling times were well chosen and extended for an adequate period of time. The method of active substance analysis was acceptable. Statistical analysis was appropriate.

It is noted that this study was conducted using the 0.2 mg meloxicam/kg bw dose. This is the loading dose after which the dose used is 0.1 mg/kg bw. It is acceptable to use the highest recommended dose as long as dose linearity is shown. It should be noted that the reference product SPC states that there is dose linearity observed across the therapeutic range. Based on comparison of $AUC_{(0-\infty)}$ and C_{max} data provided, the test and reference items are considered to be bioequivalent. It is therefore agreed that the test product is bioequivalent to the reference veterinary medicinal product for dogs. This supports the application according to article 13(1) of Directive 2001/82/EC, as amended, and therefore no pharmacodynamic, further pharmacokinetic data, target species tolerance data or clinical data are needed in support of this application.

Cats

This was a single dose, two-way cross-over bioequivalence study comparing two meloxicam oral suspension formulations at a dose of 0.1 mg/kg bw administered orally to healthy cats and was a GLP compliant two-period, two-sequence crossover study with a wash out period of 14 days. The objective was to determine the meloxicam concentrations in plasma in order to compare the single-dose bioavailability of the test item with the reference item after a single oral administration of both meloxicam containing suspensions at a target dosage of 0.1 mg meloxicam per kg bw in cats. The test article was meloxicam (0.5 mg meloxicam/ml) 0.5 mg/ml oral suspension; batch of proposed commercial formulation with a certificate of analysis provided. The reference article was Metacam (0.5 mg meloxicam/ml) 0.5 mg/ml oral suspension for cats; batch of an existing commercial formulation with a certificate of analysis.

Healthy castrated male and female adult cats were used. The number of cats used was justified in terms of knowledge available from previous dog studies as there were very little data available for cats. A high intra-animal variation was used to calculate sample size. Cats were allocated to groups based on training, weight and sex. There was an acclimatisation and training period. Each treatment period consisted of a single treatment day (a dose of 0.1mg meloxicam/kg bw), and a further 2–day follow-up period in which blood samples were taken. The cats were treated after fasting overnight and were fed post dosing. The dose was justified as being the standard dose as recommended by the reference product. The test item or reference item was administered as a once-off dose into the mouth by syringe. During the study, all cats were examined daily during treatment and follow-up to evaluate their general health status. This included food consumption observations. Bodyweight was only measured once before treatment. Blood samples for the determination of meloxicam concentration in plasma were collected before treatment prior to administration and at various time points after the administration in each treatment phase. The study protocol has included an acceptable rationale for the sampling times. It was designed around the knowledge T_{max} was approximately 3 hours, $t_{1/2}$ was 24 hours and various time points were added to detect any enterohepatic cycling. All plasma samples were stored until they were transported for analysis.

This study was well designed and conducted. Cats were appropriate subjects as they are the proposed target species. The justification for the number of cats is adequate. There was no typical randomisation. However, because this is a cross-over study design this is not a concern. The justification for planned plasma sampling times was adequate and extended for an adequate period of time. The method of active substance analysis was acceptable. Statistical analysis was appropriate.

It is noted that this study was conducted using the 0.1 mg meloxicam/kg bw dose. This is the loading dose after which the dose used is 0.05 mg/kg bw (in accordance with the reference SPC). It is acceptable to use the highest recommended dose as long as dose linearity is shown. It should be noted that the reference product SPC states that there is dose linearity observed across the therapeutic range for cats. Based on comparison of AUC_t and C_{max} the test and reference items are considered to be bioequivalent. It is agreed that the test product is bioequivalent to the reference veterinary

medicinal product for cats. This supports the application according to article 13(1) of Directive 2001/82/EC, as amended, and therefore no pharmacodynamic, further pharmacokinetic data, target species tolerance data or clinical data are needed in support of this application.

Tolerance in the target species of animal

The application is made in accordance with article 13(1) of Directive 2001/82/EC, as amended, for a generic product, and therefore data on target species tolerance are not required if bioequivalence has been demonstrated with the reference product. However the clinical expert's critical summary has made a review of the scientific literature relevant to pharmacodynamics. In view of the above, the applicant has included the same warnings in the SPC and product literature as that of the reference product, Metacam 0.5 mg/ml Oral Suspension.

CONCLUSION ON EFFICACY

The application was made in accordance with article 13(1) of Directive 2001/82/EC, as amended: an application for a generic product.

The applicant submitted a bioequivalence study comparing the proposed and the reference meloxicam 1.5 mg/ml oral suspension formulations, at a dose of 0.2 mg/kg bw administered orally, in healthy dogs. Bioequivalence between the formulations was concluded based on the $AUC_{(0-\infty)}$ and C_{max} parameters and in accordance with the relevant guideline for the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00). It is considered that bioequivalence for the 1.5 mg/ml oral suspension formulations has been demonstrated in dogs.

The applicant also submitted a bioequivalence study comparing the proposed and the reference 0.5 mg/ml meloxicam oral suspension formulations, at a dose of 0.1 mg/kg bw administered orally, in healthy cats. Bioequivalence between the formulations was concluded based on the $AUC_{(0-t)}$ and C_{max} parameters and in accordance with EMEA/CVMP/016/00. It is considered that bioequivalence for the 0.5 mg/ml oral suspension formulations has been demonstrated in cats.

5. Benefit risk assessment

Benefits

The product is considered to be appropriately formulated. It is manufactured and controlled in accordance with relevant EU and VICH quality guidelines and current scientific knowledge. The applicant has provided a written commitment to submit stability data on the first commercial scale batches of the product as soon as these are available.

The product is indicated in dogs as a 1.5 mg/ml oral suspension for alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders and in cats as a 0.5 mg/ml oral suspension for alleviation of inflammation and pain in chronic musculo-skeletal disorders. Efficacy has been demonstrated by means of bioequivalence to the reference product Metacam.

Risks

Safety to users of the product and to the target species has been demonstrated by means of bioequivalence to the reference product Metacam. There are no excipients which would indicate an increased risk. Warning statements in the SPC are therefore in line with those of the reference product.

The use of the product is not expected to pose a risk for the environment.

OVERALL BENEFIT-RISK BALANCE

The benefit-risk balance of this product is the same as the reference product and is considered acceptable.

Overall, the benefit/risk balance is considered favourable for the product.

OVERALL CONCLUSIONS

Having reviewed the data on quality, safety and efficacy, the CVMP considers that the application for Melosus, for the alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders in dogs (as a 1.5 mg/ml oral suspension) and alleviation of inflammation and pain in chronic musculo-skeletal disorders in cats (as a 0.5 mg/ml oral suspension), is approvable.

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