13 September 2018
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Rheumocam to add a new strength 0.5 mg/ml oral suspension for existing target species - cats (EMEA/V/C/000121/X/0022)

International non-proprietary name: meloxicam

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted

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Introduction

The applicant Chanelle Pharmaceuticals Manufacturing Ltd submitted on 11 May 2017 an application for an extension to the marketing authorisation for Rheumocam to the European Medicines Agency (the Agency) in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I thereof.

Rheumocam is a generic veterinary medicinal product for which the reference product is Metacam. It contains meloxicam, a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class, which acts by inhibition of prostaglandin synthesis, and was authorised for use in the Union on 10 January 2008.

Rheumocam is currently available in different pharmaceutical forms and strengths, including oral suspension for dogs (1.5 mg/ml) and horses (15 mg/ml), chewable tablets for dogs (1 mg and 2.5 mg), solution for injection for dogs, cats, cattle and pigs (5 mg/ml), solution for injection for cattle, pigs and horses (20 mg/ml), and granules for horses (330 mg).

This extension application is to add an oral suspension of 0.5 mg meloxicam/ml for cats.

The applicant applied for the following indications:

- Alleviation of mild to moderate postoperative pain and inflammation following surgical procedures in cats, e.g. orthopaedic and soft tissue surgery.
- Alleviation of pain and inflammation in acute and chronic musculoskeletal disorders in cats.

Rheumocam 0.5 mg/ml oral suspension for cats is presented in packs containing 1 bottle of either 10 ml or 15 ml of suspension.

The rapporteur appointed was Sylvie Louet and the co-rapporteur was Ellen-Margrethe Vestergaard.

The dossier has been submitted in line with the requirements for submissions in accordance with Article 19 of Commission Regulation (EC) 1234/2008 and Annex I thereof (extensions).

On 13 September 2018, the CVMP adopted an opinion and CVMP assessment report.

On 19 November 2018, the European Commission adopted a Commission Decision granting the extension to the marketing authorisation for Rheumocam.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (dated 28 June 2014), which fulfils the requirements of Directive 2001/82/EC. Based on the information provided, the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

The complete manufacture of the dosage form (manufacturing, primary and secondary packaging, batch control and batch release) takes place in ~~Ireland, at Chanelle Pharmaceuticals Manufacturing Ltd~~the European Union. Batch release takes place at Chanelle Pharmaceuticals Manufacturing Ltd, Ireland. A GMP certificate issued by the Irish Medicines Board based on an audit conducted on 7 November 2014 has been provided.

~~The manufacturer of the active substance meloxicam is AMSA S.p.A., Italy.~~ A QP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) of Chanelle Pharmaceuticals referencing the site of manufacture of the active substance ~~(AMSA in Italy)~~. The declaration is based on an on-site audit of this facility conducted on 22 November 2014.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The finished product is presented as an oral suspension for cats containing 0.5 mg/ml meloxicam.

Other ingredients are: glycerol (dispersing agent), citric acid monohydrate (buffer), xanthan gum (suspending agent), povidone (suspending agent), sodium dihydrogen phosphate monohydrate (suspending agent), sodium benzoate (preservative), simethicone emulsion (antifoaming agent), honey flavour (flavour), silica colloidal anhydrous (suspending agent) and purified water (vehicle).

Containers

The primary packaging is high density polyethylene (HDPE) bottles containing 10 ml or 15 ml with a tamper-proof child-resistant polypropylene closure. The material complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements.

Each bottle is packed in a cardboard box with a polypropylene measuring syringe. It is calibrated to deliver doses from 0.1 ml to 1.0 ml.

The presentations initially proposed by the applicant are not suitable in all cases (e.g. too big for treatment of acute musculoskeletal disorders or for treatment of little cats). Therefore, the applicant was requested to add a smaller presentation (a bottle of 5 ml) during assessment. In response to this request, the applicant proposed smaller presentations of 3 ml and 5 ml, indicating that necessary data will be submitted when available. The CVMP concluded that there were insufficient data to support the authorisation of these 2 new presentations at the time of this line extension, but accepted that this proposal from the applicant to add them would satisfactorily address the question raised. The CVMP therefore recommends to the applicant that variations should be submitted to add the smaller presentations as soon as the supporting stability data becomes available.

Development pharmaceutics

The product has been formulated to be bioequivalent to the reference product Metacam 0.5 mg/ml oral suspension for cats and contains the same concentration of active substance (meloxicam) used in the reference product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. The excipients included in the formulation are commonly used in veterinary medicinal products. The list of excipients is included in section 6.1 of the SPC.

The oral suspension contains a preservative (sodium benzoate) and efficacy of antimicrobial preservation has been demonstrated at the low level proposed in the specification of the finished product (i.e. 80% of the nominal content).

Method of manufacture

The manufacturing process consists of several steps: dissolution or dispersion of the ingredients steps, and filling step.

The process is considered to be a non-standard manufacturing process since the finished product is a suspension.

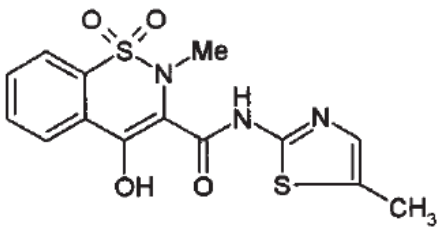
Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

The validation of the manufacturing process has been conducted on 2 production-scale batches (smallest proposed batch size), but process validation will be conducted on ~~900 l batches (~~the largest proposed batch size~~)~~ prior to first release into the marketplace, which is considered acceptable.

Control of starting materials

Active substance

The chemical name of meloxicam is 4-hydroxy-2-methyl-N-(5-methyl-1,3-thiazol-2-yl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide and the substance has the following structure:



The active substance meloxicam is a pale yellow powder, non-hygroscopic and insoluble in water.

Meloxicam has a non-chiral molecular structure.

Polymorphism has been observed for meloxicam (5 crystalline forms are reported), but it has been demonstrated that meloxicam produced by ~~AMSA~~ the active substance manufacturer is ~~polymorph I~~always the same polymorph.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

There is a monograph of meloxicam in the Ph. Eur. The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for residual solvents and particle size. All additional methods have been adequately validated and described.

The characterisation of the active substance and its impurities is in accordance with the CVMP guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are considered satisfactory.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it has been considered satisfactory. However, the redefinition of the starting materials is recommended post-authorisation which has been agreed by the ASMF holder.

The ASMF contains information both on standard and micronised meloxicam powder, and the applicant has confirmed that meloxicam that is used in the manufacture of the finished product is not micronised.

Batch analysis data of 3 batches of ~~(n=6 and scale: 898 kg, 852 kg and 937 kg for~~ non-micronised meloxicam and 3 batches of ~~270 kg, 520 kg and 302 kg for~~ micronised meloxicam~~)~~ ~~of the active substance~~ have been provided. The results are within the specifications and consistent from batch to batch.

Stability data on 3 batches of active substance stored in double polyethylene bags contained in miniature drums for 60 months under long-term conditions at 25 °C/60% RH and for up to 6 months under accelerated conditions at 40 °C/75% RH according to the VICH guidelines were provided. From the

stability data provided for meloxicam, ~~a~~ the proposed retest period ~~of 5 years without special~~and storage conditions ~~is~~ are acceptable.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur or USP standards, except honey flavour, for which scientific data including composition, specifications and certificates of analysis are provided and are considered acceptable.

The list of excipients is included in section 6.1 of the SPC.

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

None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev 3). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

Control tests on the finished product

The proposed specifications conform to the requirements of the Ph. Eur. monograph 0672 Liquid preparations for oral use. The finished product is tested at release for appearance, condition of packaging, identification and assay of active substance, pH, viscosity, identification and assay of preservative, test for resuspension, microbial purity and particle size. The absence of dissolution testing has been justified. The specifications proposed for use at release are appropriate to control the quality of the finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with the VICH guidelines.

Batch analysis results are provided for two batches ~~of 90 l~~ confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Stability data of 2 batches of finished product stored under long-term conditions for 18 months at 25 °C/60% RH and for up to 6 months under accelerated conditions at 40 °C/75% RH according to VICH GL3 were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing (10 and 15 ml).

Samples were tested for appearance, condition of packaging, identification and assay of active substance, pH, viscosity, preservative assay, microbial purity, related substances, resuspension and particle size. For the tests performed up to 18 months at 25 °C/60% RH and up to 6 months at 40 °C/75% RH, no significant changes have been observed, with the exception of the results for preservative content which decrease during the storage.

Based on the available stability data, the proposed shelf life of 30 months is accepted.

An in-use shelf life of 3 months has been adequately justified.

Overall conclusions on quality

Information on the development, manufacture, control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE (transmissible spongiform encephalopathy) safety.

A recommendation is made for the applicant to submit variations to add the two smaller presentation sizes of 3 ml and 5 ml as soon as the supporting stability data becomes available.

Part 3 – Safety

The product is an oral suspension intended for use in cats, with meloxicam as the active ingredient. Meloxicam has been developed as an anti-inflammatory and anti-rheumatic for cats and has been well known in veterinary medicine for more than 10 years.

Safety documentation

The absence of toxicological and tolerance data is acceptable as bioequivalence is established between the reference product (Metacam 0.5 mg/ml oral suspension for cats) and the candidate product (Rheumocam 0.5 mg/ml oral suspension for cats). In this context, results of toxicological and tolerance tests are not required, since they are assumed to be identical to those of the reference product.

The applicant has provided a User Safety Assessment and a Phase I Environmental Impact Assessment.

Toxicological studies

As bioequivalence with the reference product is established, results of toxicological tests are not required.

Tolerance in the target species of animal

The tolerance in the target animal is described under Part 4.

Excipients

The excipients used in the formulation are well established with an extensive history of use in oral formulations. Given the known use of the excipients and the expected safety profile, it is not expected that the excipients will present a hazard to either the target animal or the user.

User safety

Rheumocam contains additional excipients compared to the reference product. Thus, the applicant presented a qualitative risk assessment to determine if any of these have any impact on the risk that the generic product may pose to users, including children.

Taking into account that:

- the concentration of active substance is identical in the test and reference products;
- the pharmaceutical form, the target species, the therapeutic scheme and the route of administration are identical between both products;
- the limited differences of formulation with Metacam 0.5 mg/ml suspension for cats have no impact on the absorption of the product;
- excipients in Rheumocam are widely used in oral formulations for veterinary medicinal products and their safety is considered acceptable;
- the exposure of the user to the test and the reference products is similar;

it can be concluded that the potential risks to the user following the use of Rheumocam 0.5 mg/ml oral suspension are identical to those following the use of Metacam 0.5 mg/ml oral suspension. Proposed warning sentences, identical to the reference product, are appropriate and sufficient to ensure the safety of users, including children.

Environmental risk assessment

The Environmental Risk Assessment (ERA) of the pharmaceutical product was performed according to the relevant guidelines (VICH GL6 and GL38 and CVMP Guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1).

The conclusion is supported that the ERA can stop at phase I, and no phase II is required because the veterinary medicinal product will only be used in non-food producing animals.

The product is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Since this is a generic product and bioequivalence with the reference product is demonstrated, results of toxicological tests are not required.

The new excipients used in the formulation are well known and widely used in pharmaceutical products intended for human and veterinary use.

Based on the user safety assessment and the type of application it is acceptable to keep the same mitigation measures as those present in the SPC of the reference product.

The environmental risk assessment can stop at phase I. The product is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Pharmacodynamics / Pharmacokinetics

Since this is a generic product and bioequivalence with the reference product has been demonstrated, results of pharmacological tests are not required.

The pharmacological aspects of this product are identical to those of the reference product.

Development of resistance

Not applicable.

Bioequivalence studies

The applicant has provided an *in vivo* study in cats to investigate the bioequivalence between the test product and the reference product (Metacam 0.5 mg/ml oral suspension for cats).

The two formulations were compared after a single oral administration of 0.2 mg/kg body weight to cats (n=12 per group, aged 1-2 years) according to a cross-over design with a wash-out period of 14 days. Animals were fasted at least 12 hours before each administration. Food was given 30 min after administration. The study is in line with CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-Rev.2) and VICH GL52 on Bioequivalence: blood level bioequivalence study. The cats were observed several times daily for appearance and behaviour, and blood samples were taken before treatment up to 96 hours post dosing.

During the trial, gastrointestinal signs were noted in some animals (diarrhoea, salivation, vomiting, faeces containing mucus and/or blood), confirming the narrow margin of safety recognised previously in cats.

The values of area under the curve (AUC_t and $AUC_{0\text{-infinity}}$) were 17454.7 and 18521.5 ng.h/ml, respectively, for Rheumocam, and 19402.6 and 19923.3 ng.h/ml, respectively, for the reference product. The 14-day wash-out period was considered sufficiently long, and the 90% confidence intervals for the ratio of population means (test/reference) for AUC and C_{max} fell within the bioequivalence acceptance limits of 80-125% and 70-143%, respectively. The maximum observed concentration (C_{max}) and time (median) when C_{max} was observed (T_{max}) were 647.08 ng/ml and 6 [3-9] hours for Rheumocam, compared to 840.81 ng/ml and 3 [1-12] hours for the reference product. The applicant has justified the widened confidence interval for C_{max} (71.00-83.41) because of the known variability of this parameter after oral administration of meloxicam.

Bioequivalence has been demonstrated between Rheumocam and the reference product Metacam oral suspension in cats and therefore Rheumocam is expected to be as safe and efficacious as the reference product.

Dose determination / finding studies

Not applicable.

Dose confirmation studies

Not applicable.

Target animal tolerance

Since this is a generic product and bioequivalence with the reference product has been demonstrated, results of tolerance tests are not required. Moreover, the excipients used in the product are well known and widely used in other pharmaceutical products. Furthermore, except transient gastrointestinal side effects, which are known adverse effects with NSAIDs and which support the narrow margin of safety recognised previously in cats, no serious adverse effects were reported in the bioequivalence study.

As bioequivalence has been demonstrated, the expected tolerance profile in the field is considered to be the same as that of the reference product.

Clinical field trials

No clinical efficacy studies were provided. Given the nature of the application, this is considered acceptable since bioequivalence with the reference product has been demonstrated.

Overall conclusion on efficacy

Rheumocam 0.5 mg/ml oral suspension for cats is a generic product and this application was submitted according to Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I thereof (extensions). Rheumocam and its reference product, Metacam, are both aqueous oral suspensions containing the same concentration of active substance. The applicant has provided an *in vivo* bioequivalence study in cats comparing the two formulations (Rheumocam and Metacam). As bioequivalence has been demonstrated, the generic product is expected to have similar safety and efficacy profiles and the same indications and posology as the reference product.

Part 5 – Benefit-risk assessment

Introduction

Rheumocam 0.5 mg/ml oral suspension for cats is a generic veterinary medicinal product, containing meloxicam as active substance.

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class and acts by inhibition of prostaglandin synthesis. The product is intended for use in cats for the alleviation of mild to moderate postoperative pain and inflammation following surgical procedures in cats, e.g. orthopaedic and soft tissue surgery, and the alleviation of pain and inflammation in acute and chronic musculoskeletal disorders in cats.

Rheumocam is currently available in different pharmaceutical forms and strengths for different species (including a solution for injection for cats); this extension application is to add a new pharmaceutical form (oral suspension) and strength (0.5 mg/ml) for cats.

The dossier has been submitted in line with the requirements for submissions in accordance with Article 19 of Commission Regulation (EC) 1234/2008 and Annex I thereof (extensions).

Benefit assessment

Direct therapeutic benefit

The benefit of Rheumocam 0.5 mg/ml oral suspension would be to allow oral treatment of cats for the alleviation of mild to moderate postoperative pain and inflammation following surgical procedures, e.g. orthopaedic and soft tissue surgery, and for the alleviation of pain and inflammation in acute and chronic musculoskeletal disorders.

Since Rheumocam 0.5 mg/ml oral suspension for cats is a generic product, its direct therapeutic benefits are expected to be the same as those for the reference product Metacam 0.5 mg/ml oral suspension for cats. The evidence for the direct therapeutic benefit is considered established, based on the results of a bioequivalence study confirming bioequivalence between Rheumocam 0.5 mg/ml oral suspension and the reference product.

Additional benefits

None identified.

Risk assessment

Quality:

Information on development, manufacture, control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety:

Risks for the target animal:

Since bioequivalence with the reference product has been demonstrated and excipients of the tested product are well known and widely used in other pharmaceutical products, the risks associated with the use of the product in the target species are the same as those of the reference product.

Adverse reactions of NSAIDs such as loss of appetite, vomiting, diarrhoea, faecal occult blood, lethargy and renal failure have been reported. In very rare cases, gastrointestinal ulceration and elevated liver enzymes have been reported. These side effects are in most cases transient and disappear following termination of the treatment, but in very rare cases may be serious or fatal.

Risk for the user:

A user risk assessment has confirmed that the use of the product does not entail a greater risk for the user than the reference product. The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations.

Risk for the environment:

Rheumocam 0.5 mg/ml oral suspension for cats is not expected to pose a risk for the environment when used according to the SPC.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform of the potential risks of this product relevant to the target animals, users and the environment and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

Based on the data presented, the overall benefit-risk balance is considered positive.

The applicant applied for the following indication: "Alleviation of mild to moderate postoperative pain and inflammation following surgical procedures in cats, e.g. orthopaedic and soft tissue surgery. Alleviation of pain and inflammation in acute and chronic musculoskeletal disorders in cats."

The product has been shown to be efficacious for the alleviation of pain and inflammation and the CVMP agreed to the indications proposed by the applicant.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) considers that the application for Rheumocam 0.5 mg/ml oral suspension for cats is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the extension of the marketing authorisation for Rheumocam to include Rheumocam 0.5 mg/ml oral suspension for cats.