13 March 2025
EMA/110849/2025
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a variation requiring assessment for Rheumocam (EMEA/V/C/000121/VRA/0038)

INN: Meloxicam

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

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Introduction

Submission of the variation application

In accordance with Article 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Chanelle Pharmaceuticals Manufacturing Ltd (the applicant), submitted to the European Medicines Agency (the Agency) on 3 May 2024 an application for a variation requiring assessment for Rheumocam.

Scope of the variation

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 already authorised in different pharmaceutical forms and strengths, including oral suspension for cats (0.5 mg/ml), 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 variation is to add a new strength to the existing Rheumocam range of products: 2 mg/ml solution for injection for cats which is presented in packs containing 1 vial with either 10 ml or 20 ml of solution for injection.

Variation(s) requested	
I.II.1.c	Changes to strength, pharmaceutical form and route of administration - Change or addition of a new strength/potency

At the time of submission, the applicant applied for the following indication: Alleviation of mild to moderate post-operative pain and inflammation following surgical procedures in cats, e.g. orthopaedic and soft tissue surgery.

Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 2, Part 3 and Part 4.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided an updated summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF) with reference number PSMFCPML5666, has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

- Option 1

A declaration has been provided for the active substance manufacturer from the QP at the proposed EU batch release site Chanelle stating that the active substance is manufactured in compliance with EU GMP. The QP declaration also references an audit of the manufacturing site of the active substance.

- Option 2

Activities performed: manufacture of active substance intermediate 2-amino-5-methylthiazole

Activities performed: manufacture, micronisation, packaging, quality control testing, storage and distribution of the active substance.

A declaration has been provided for the active substance manufacturer from the QP at the proposed EU batch release site Chanelle stating that the active substance is manufactured in compliance with EU GMP. The QP declaration also references an audit of the manufacturing site of the active substance intermediates .

Finished product

Site No 1

Activities performed at manufacturing site: manufacture of dosage form, quality control testing (chemical/physical and microbiological), primary packaging and secondary packaging.

Manufacturing Authorisation was issued on 14 February 2024 by the Spanish Competent Authority (source: EudraGMP)

A GMP certificate confirming compliance with the principles of GMP is provided. The certificate was issued on 24 October 2021, referencing an inspection on 16 September 2021, by the Spanish Competent Authority.

Site No 2

Chanelle Pharmaceuticals Manufacturing

Ida Industrial Estate
Dublin Road
Loughrea
Co. Galway
H62 FH90
Ireland

Activities performed:Batch release.

Manufacturing Authorisation was issued on 18 January 2024 by the Irish Competent authority.

A GMP certificate confirming compliance with the principles of GMP is provided. The certificate was issued on 18 March 2024, referencing an inspection on 21 April 2023, by the Irish Competent Authority.

Site No 3

Activities performed: quality control testing (microbiological).

A GMP certificate confirming compliance with the principles of GMP is provided. The certificate was issued on 9 August 2022, referencing an inspection on 20 July 2022, by the Irish Competent Authority.

Overall conclusions on administrative particulars

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

The summary of pharmacovigilance system master file was considered to be in line with legal requirements.

Part 2 - Quality

Composition

The finished product is presented as a solution for injection containing 2 mg/ml of meloxicam as active substance.

Other ingredients are: ethanol anhydrous, meglumine, macrogol 300, poloxamer 188, glycine, disodium edetate, sodium hydroxide, hydrochloric acid concentrated and water for injections.

The solution is packaged in type I clear glass vials containing either 10 or 20 ml of solution for injection. The vials are closed with a bromobutyl rubber stopper and an aluminium flip-off capsule.

The pack sizes are consistent with the dosage regimen and duration of use.

Containers and closure system

The primary packaging are type I clear glass vials closed with a bromobutyl rubber stopper and an aluminium flip-off capsule.

The material complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. The choice of the container closure system has been validated by stability data.

The applicant has provided data to demonstrate that the stopper complies with the requirements of Ph. Eur. 3.2.9 for self-sealing and fragmentation tests after 30 punctures per vial. Based on the posology the stopper is not intended to be punctured more than 30 times. Therefore, the absence of a statement regarding the maximum number of piercings in section 3.9 of the SPC is accepted.

Product development

The aim of this development is to obtain a generic formulation of Metacam 2 mg/ml solution for injection for cats (EU/2/97/004/039 and EU/2/97/004/040) from Boehringer Ingelheim Vetmedica GmbH, with the same qualitative and quantitative formula and being bioequivalent. The proposed product has the same qualitative and similar quantitative composition as the formulation of the reference product. The comparison of the physicochemical properties shows that both the reference and the proposed product have similar density, pH and appearance.

The efficacy of antimicrobial preservation test has been performed using the lowest limit of ethanol content proposed in the specification of the finished product and in line with Ph. Eur. 5.1.3.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC.

Description of the manufacturing method

The manufacturing process consists of 4 main steps: bulk preparation, bulk filtration, filling and terminal sterilisation following Ph. Eur. conditions. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies on the smallest commercial batch size. 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 type of manufacturing process.

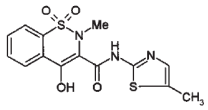
It is accepted that process validation on larger scale batches will be performed post-authorisation.

Acceptable validation data has been submitted for the proposed holding time before filling.

Control of starting materials

Active substance

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



The meloxicam is a pale-yellow powder, practically insoluble in water, slightly soluble in acetone and soluble in dimethylformamide.

Meloxicam has a non-chiral molecular structure.

The information on the active substance is provided according a Certificate of Suitability of the European Pharmacopoeia (CEP) for one supplier and according to the Active Substance Master File (ASMF) procedure for another supplier.

Supplier with CEP

There is a monograph of meloxicam in the Ph. Eur., and the ASMF holder has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for meloxicam, a copy of which has been provided within the application. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. 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 solvents and particle size. All additional methods have been adequately validated and described according to relevant guideline. The CEP indicates a re-test period of 60 months when stored a double polyethylene bag (outer black), placed in a polyethylene drum.

According to the CEP for meloxicam, water is used as solvent in the last steps of the synthesis. The applicant should confirm that the water used is purified water and that appropriate specifications have been set for endotoxins and microbiological quality of the active substance, according to the Guideline on the quality of water for pharmaceutical use (EMEA/CHMP/CVMP/QWP/496873/2018).

Supplier with ASMF procedure

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Polymorphism has been observed for meloxicam. This active substance manufacturer produces polymorph I.

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.

The analytical methods used have been adequately described and appropriately validated in accordance with the VICH guidelines VICH GL2. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

Stability data for batches of active substance from the proposed manufacturer stored in double layer polyethylene bags, were provided for 60 months under long term conditions at 25 ºC/60% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH guidelines.

The following parameters were tested: appearance, related substances, loss on drying, assay by HPLC and potentiometric titration.

All tested parameters were within the specification. The impurity levels are generally low and not increasing with time.

The stability results justify the proposed retest period in the proposed container.

Finished product manufacturer

A single specification for the active substance is applied by the finished product manufacturer which is in line with the Ph. Eur. monograph for meloxicam and with the specifications set by the 2 active substance suppliers. Since the finished product is sterile a test and limits for microbial quality in line with Ph. Eur 5.1.4. have been included in the specification of the active substance applied by the finished product manufacturer.

Certificates of analysis from the finished product manufacturer have been provided.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC.

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

The product does not contain any materials derived from human or animal origin.

Control tests on the finished product

The finished product specification includes tests for: appearance, colour of the solution, clarity of the solution, extractable volume, visible particles, density, pH, active substance identification, active substance assay, degradation products, preservative identification and assay, and sterility.

The specifications proposed at release are generally appropriate to control the quality of the finished product.

The potential presence of elemental impurities in the finished product has been satisfactorily assessed.

The analytical methods used have been adequately described and appropriately validated in accordance with the VICH guidelines. Satisfactory information regarding the reference standards used for active substance and preservative assays has been presented.

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

Stability

The specifications of the finished product proposed at the end of shelf-life are the same as those proposed at release.

Stability results of finished product are available up to 6 months in long term and in accelerated conditions, and they comply with the specifications. Based on these results a shelf life of the veterinary medicinal product as packaged for sale is 1 year.

In use stability results complies with the specifications up to 28 days after opening.

Based on photostability results, the finished product should be protected from light.

Overall conclusions on quality

Rheumocam is a generic veterinary medicinal product of Metacam. This variation is to add a new strength, Rheumocam 2 mg/ml solution for injection for cats which is presented in packs containing 1 vial with either 10 ml or 20 ml of solution for injection.

The qualitative composition is the same as that of Metacam 2 mg/ml solution for injection for cats and quantitatively very similar. It is a multidose product and efficacy of antimicrobial preservation of the formulation has been satisfactorily demonstrated.

The active substance is provided by 2 different suppliers which are already authorised for other strengths and pharmaceutical forms of Rheumocam. The finished product manufacturer applies a single specification of the active substance compliant with the Ph. Eur. monograph for meloxicam and in line with the specifications set by both active substance suppliers. The finished product manufacturer has also included a test for microbial quality of the active substance given that it is used in a sterile pharmaceutical form.

The excipients are all compliant with Ph. Eur. The product does not contain any materials derived from human or animal origin.

The manufacturing process of the finished product is considered standard. It is terminally sterilised in line with Ph. Eur. conditions. Process validation data have been provided for the smallest commercial batch size. It is accepted that process validation of the largest commercial size batch is performed post-authorisation.

The specification proposed to control the finished product is adequate for this pharmaceutical form. The analytical methods used have been adequately described and appropriately validated in accordance with the VICH guidelines where relevant. Batch data has been submitted and results are within the specifications.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the VMP throughout its shelf life when stored under the approved conditions.

The in-use shelf life of the broached VMP is supported by the data provided. The recommendations in the product leaflet should be followed.

Part 3 – Safety documentation

Rheumocam is a generic of Metacam and this variation is to add a new strength (2 mg/ml) as solution for injection for cats. The reference product is Metacam 2 mg/ml solution for injection for cats (EU/2/97/004/039-040). Rheumocam contains meloxicam as active ingredient. Meloxicam has been developed as anti-inflammatory in cats and has been used in veterinary medicine for more than 10 years.

Cross-reference is made to data from 'Metacam 2 mg/ml solution for injection for cats'. No new data on safety were submitted, except for data on the user risk assessment. Only these new data have been assessed in the frame of the present application.

Safety tests

Given that bioequivalence is established between the reference product and the candidate product, results of toxicological and tolerance tests are not required, since a generic product may rely on the results of the appropriate safety, residue, pre-clinical and clinical studies of the reference product.

The applicant has provided a user safety assessment and a Phase I environmental risk assessment (ERA) in accordance with to the relevant guidelines (see below).

Pharmacology

See part 4A.

Toxicology

Given that bioequivalence with the reference product can be accepted (see part 4), the submission of toxicological data is not required.

Tolerance in the target species

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

Excipients

'Rheumocam 2 mg/ml solution for injection for cats' and the reference product contain the same excipients in similar quantities. They are currently widely used in veterinary medicines and do not raise any toxicological concern for the target species and the user.

User safety

The risks for the user handling this veterinary medicinal product are expected to be the same as those of the reference product, and the warnings in the product information for the reference product can be considered adequate as regards the potential risks. However, the applicant has presented a user safety assessment in accordance with the 'CVMP Guideline on user safety for pharmaceutical veterinary medicinal products' (EMA/CVMP/543/03-Rev.1).

It is concluded that the potential risks to the user following the use of 'Rheumocam 2 mg/ml solution for injection for cats' are identical to those following the use of 'Metacam 2 mg/ml solution for injection for cats'. Therefore, the advice provided in the SPC for 'Rheumocam 2 mg/ml solution for injection for cats' should be the same as that presented for 'Metacam 2 mg/ml solution for injection for cats'.

Environmental risk assessment

The ERA of the pharmaceutical product was performed according to the relevant guidelines (VICH GL6 and the '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 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: safety tests

Bioequivalence with the reference product is established, and therefore, results of pharmacological or toxicological tests are not required.

A user risk assessment and an environmental risk assessment have been provided.

'Rheumocam 2 mg/ml solution for injection for cats' and the reference product contain the same excipients in similar quantities. They are currently widely used in veterinary medicines and do not raise any toxicological concern for the target species and the user.

Based on the type of application, the risk mitigation measures pertaining to user safety are identical to those approved for 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

Pre-clinical studies

Rheumocam is a generic of Metacam and this variation is to add a new strength (2 mg/ml) as solution for injection for cats. The reference product is Metacam 2 mg/ml solution for injection for cats (EU/2/97/004/039 and EU/2/97/004/040). Rheumocam contains meloxicam as active ingredient. Meloxicam has been developed as an anti-inflammatory in cats and has been used in veterinary medicine for more than 10 years.

Pharmacology

Pharmacodynamics

No pharmacodynamic studies were presented, as bioequivalence with the reference product has been demonstrated. The omission of pharmacodynamic data is considered acceptable given the legal basis of the application.

The pharmacodynamic properties of the active substance are detailed in section 4.2 of the SPC and are identical to those approved for the reference product.

Bioequivalence studies

No *in vivo* bioequivalence studies are provided. Both the generic product and the reference product are intended for subcutaneous use.

The absence of bioequivalence data is in line with waiver requirement 7.1 b) of the CVMP guideline on bioequivalence (EMA/CVMP/016/2000-Rev4.) as the generic product is of the same type of solution, contains the same concentration of the active substance and the same excipients in similar amounts as the reference veterinary medicinal product. The resulting pH is the same.

In conclusion, both products are considered bioequivalent.

Tolerance in the target animal species

Considering that bioequivalence with the reference product is demonstrated and that the 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 for the reference product. The special precautions for safe use in the target species present in the SPC are identical to the ones of the reference product.

Clinical trial(s)

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

Overall conclusions on efficacy

Given that bioequivalence with the reference product is established, data from clinical efficacy studies are not required. It can be expected that both Rheumocam 2 mg/mL solution for injection for cats and the reference product will have a similar safety and efficacy profile for the same indications and posology.

Part 5 – Benefit-risk assessment

Introduction

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 already authorised in different pharmaceutical forms and strengths, including oral suspension for cats (0.5 mg/ml), 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).

The proposed variation is to add a new strength 2 mg/ml solution for injection for cats for alleviation of mild to moderate post-operative pain and inflammation following surgical procedures, e.g. orthopaedic and soft tissue surgery.

Rheumocam 2 mg/ml solution for injection for cats is presented in packs containing 1 vial with either 10 ml or 20 ml of solution for injection.

The application has been submitted in accordance with Article 62 of Regulation (EU) 2019/6.

Benefit assessment

Direct benefit

The benefit of Rheumocam 2 mg/ml solution for injection for cats would be its efficacy for alleviation of mild to moderate post-operative pain and inflammation following surgical procedures, e.g. orthopaedic and soft tissue surgery.

Since Rheumocam 2 mg/ml solution for injection for cats is a generic product, its direct therapeutic benefits are expected to be the same as those for the reference product. The evidence for the direct therapeutic benefit is considered established since bioequivalence to the reference product is demonstrated.

Additional benefits

None identified.

Risk assessment

Quality:

In general, information on development, manufacture, control of the active substance and finished product has been presented in a satisfactory manner.

Safety:

Risks for the target animal:

Considering that bioequivalence with the reference product is demonstrated and that the 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 for the reference product.

Risk for the user:

The proposed user warnings by the applicant are identical from those of the reference product. It is accepted that the candidate product has a similar user risk profile than the reference product and that no further assessment is required for the candidate product. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the VMP.

Risk for the environment:

Rheumocam 2 mg/ml solution for injection 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

The product can be considered efficacious for the claimed indication:

Alleviation of mild to moderate post-operative pain and inflammation following surgical procedures in cats, e.g. orthopaedic and soft tissue surgery.

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.

The product 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.

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

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 variation to the terms of the marketing authorisation for Rheumocam can be approved, since the data satisfy the requirements as set out in the legislation (Regulation (EU). 2019/6), as follows: addition of a new strength for cats, Rheumocam 2 mg/ml solution for injection for cats.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above-mentioned medicinal product.

Changes are required in the following Annexes to the Union marketing authorisation: I, II, IIIA and IIIB. Please refer to the separate product information.