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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Rheumocam (EMEA/V/C/121/X/008)

International non-proprietary name: Meloxicam

Scope: New strength and new target species (cats)

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

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Introduction

An application for an extension of a Community marketing authorisation of Rheumocam has been submitted to the European Medicines Agency (the Agency) on 26 January 2011 by Chanelle Pharmaceuticals Manufacturing Limited in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I thereof.

On 24 January 2012 the European Commission issued a Commission Decision for this extension.

This Rheumocam extension concerns a new strength, meloxicam 5 mg/ml solution for injection for dogs and cats (cats also being a new target species) and is presented in containers of 10 ml, 20 ml and 100 ml. It is indicated in dogs for the alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders and the reduction of post-operative pain and inflammation following orthopaedic and soft tissue surgery, and in cats for the reduction of post-operative pain after ovariohysterectomy and minor soft tissue surgery. The route of administration is intravenous and subcutaneous in dogs and subcutaneous in cats. The target species are dogs and cats.

Part 1 - Administrative particulars

GMP certificates (2009) for the manufacturers of the final product were issued by the Irish and Dutch authorities and no inspections are required. The active substance manufacturer is the same for those products already approved and no inspections are required.

Detailed description of the pharmacovigilance system

The applicant provided a version 6 description of the pharmacovigilance system which is very similar to version 5. It is considered to fulfil the requirements of the current legislation of the European Union.

Part 2 - Quality

Composition

Rheumocam 5 mg/ml solution for injection for dogs and cats is a generic medical product of a reference product and contains 5 mg/ml of meloxicam as active ingredient and 159.8 mg/ml of ethanol (96 per cent) as antimicrobial preservative.

Container

The product is presented in colourless glass injection vials, closed with a bromobutyl rubber stopper and an aluminium cap. It will be available in pack sizes of 10 ml, 20 ml and 100 ml.

Development pharmaceutics

Rheumocam 5 mg/ml solution for injection for dogs and cats has been formulated to closely resemble the reference product Metacam 5 mg/ml solution for injection for dogs and cats. Some changes were made in regard of the excipients, namely glycofurol is replaced by Macrogol 400, hydrochloric acid by sodium chloride and disodium edetate is present additionally.

Method of manufacture

The typical batch size may vary from 250 litres to 2500 litres. The manufacturing process consists in mixing ingredients, adjusting pH of the obtained solution, filtering the solution, filling the solution in vials and sterilising the filled vials at 121 °C for 15 minutes.

The finished product is manufactured according to a standard process in which the in-process controls are planned at three steps: preparation of the ingredients, filtration of the solution, filling of the vials. The description of the manufacturing process and the proposed in-process control are satisfactory. The validation of the manufacturing process has been conducted on two industrial batches of 500 litres. According to the provided data on validation, the manufacturing process of the finished product Rheumocam 5 mg/ml is considered validated.

Control of starting materials

Active substance

The active substance, meloxicam is described in the European Pharmacopoeia (Ph. Eur.) and manufactured at AMSA S.p.A. in Italy. Data for meloxicam have been submitted in an Active Substance Master File which has been assessed for previous applications for Rheumocam oral solution, Rheumocam tablets and Rheumocam solution for injection.

Excipients

All the excipients are described in the Ph. Eur. and are controlled according to their corresponding monographs.

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

None of the starting materials used for the production of the finished product fall within the scope of the guidance “Note for guidance on minimising the risk of Transmitting animal Spongiform Encephalopathy agents via Human and Veterinary Medicinal Products” (EMEA/410/01 rev.3).

Control tests on the finished product

The specifications proposed at release and at the end of shelf-life are appropriate to control the quality of the finished product. The description and the validation of the methods used for the control of the finished product were provided. The results of the analysis of finished product are presented and comply with the required specification.

Stability

The proposed retest period for the active substance is 5 years, stored in polyethylene bags in fibre drums. Results from storage of batches of the substance for up to 60 months at 25 °C/60%RH and 30 °C/70%RH and for 6 months at 40 °C/75%RH are available. No relevant changes were observed. The proposed retest period is considered acceptable.

Concerning finished product, based on the presented stability test results, the proposed shelf-life of 3 years is accepted.

Photostability study shows slight degradation of the finished product in vials exposed directly to light. Therefore, the sentence *Keep vial in the outer carton* has been added in the section 6.4 of the SPC.

The proposed in-use shelf-life of 28 days is accepted. The applicant has agreed to repeat the in-use stability study on a batch of finished product approaching the end of its shelf-life.

Overall conclusions on quality

The quality of the product as described in the dossier is acceptable.

Part 3 – Safety

Safety documentation

This application is made in accordance with Article 13.1(a) (iii) of Directive 2001/82/EC, as amended (a generic). Although the list of excipients for Rheumocam is not strictly similar to these of Metacam, all of them are commonly used in human and veterinary medicinal products and their toxicological profiles are well known. They should not raise particular toxicological concern for the safety of the user, the target animals and for the environment.

In support of the application, the applicant conducted two *in vivo* bioequivalence studies to show bioequivalence between the test product Rheumocam 5 mg/ml solution for injection for dogs and cats and the reference product for dogs and cats. Both studies have been reported and commented on in Part 4 of the assessment report.

Given that Rheumocam 5 mg/ml solution is bioequivalent with the reference product Metacam 5 mg/ml solution for injection in dogs and cats, the toxicological profile of meloxicam does not need to be reassessed.

Pharmacodynamics

See Part 4.

Pharmacokinetics

See Part 4.

User safety

The applicant provided a user risk assessment which was conducted in accordance with the current guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-FINAL).

Given that the limited difference of formulation with Metacam 5 mg/ml solution for injection for dogs and cats has no impact on the absorption of the product, that the excipients included in the formulations can be considered safe and that therapeutic schemes and indications are identical to those of the reference product, it can be accepted that the potential hazard to the user posed by Rheumocam 5 mg/ml solution for injection for dogs and cats will be the same as posed by the reference product. Therefore, the proposed user safety statements are considered appropriate as they are the same as for the reference product.

Environmental risk assessment

In line with the Guideline on Environmental Impact Assessment for Veterinary Medicinal Products – Phase I (CVMP/VICH/592/98-FINAL), given that the product is:

- for individual treatment under veterinary prescription,
- the product is indicated for non-food animals that are not intensively reared,

the environmental risk assessment can stop at Phase I. It is expected that the product will not pose a risk to the environment when used as recommended.

The same disposal advice is proposed for inclusion in the SPC as approved for the reference products.

Overall conclusions on the safety documentation

As this is a generic application and bioequivalence with the reference product has been established for dogs and cats, this part is sufficiently documented. It can be concluded that the safety of Rheumocam 5 mg/ml solution for injection for dogs and cats will be the same as for the reference product.

The same warning sentences for the user as for the reference product will be included in the SPC which are sufficient to ensure the safety of the person who will administer the product.

The product is not expected to pose a risk for the environment when used as recommended. The standard disposal advice as for the reference product will be included in the SPC.

Part 4 – Efficacy

Some published studies were provided by the applicant to document the pharmacodynamic properties of the active substance, meloxicam. As it is a generic application sections 5.1 and 4.2 of the SPC are similar for the test product and the reference product.

Given that bioequivalence between the test and reference products has been demonstrated for dogs and cats, and that the excipients of the test product are not expected to raise toxicological concerns for the animal safety, no specific tolerance studies, in order to determine margins of safety in the target species, are required.

A GLP bioequivalence study was performed in dogs between Metacam 5 mg/ml solution for injection for dogs and cats and Rheumocam 5 mg/ml solution for injection for dogs and cats following a single subcutaneous administration of meloxicam at 0.2 mg/kg bw. The analytical method is fully validated. The real administered dose is equal to the theoretical dose (i.e. 0.2 mg/kg bw). The study demonstrates that the two products are bioequivalent in dogs following subcutaneous administration. In the dog, the expected efficacy and tolerance of Rheumocam 5 mg/ml injectable solution is the same of the reference product.

A bioequivalence study was performed in cats between Metacam 5 mg/ml solution for injection for dogs and cats and Rheumocam 5 mg/ml solution for injection for dogs and cats following a single subcutaneous administration of meloxicam at 0.2 mg/kg bw.

The bioequivalence between the two products Rheumocam and Metacam is also demonstrated in cats.

In the cat, it is thus also possible to conclude that the expected efficacy and clinical tolerance of Rheumocam 5 mg/ml injectable is the same as that of the reference product.

Overall conclusion on efficacy

Given that this product is a generic medicinal product and that the applicant has demonstrated bioequivalence with the reference product for dogs and cats, it is accepted that the efficacy profile and the clinical tolerance of the test and reference product will be comparable.

Part 5 – Benefit risk assessment

The application for Rheumocam 5 mg/ml solution for injection for dogs and cats is a generic application. The active ingredient is meloxicam. The product was developed in such a way as to closely resemble the formulation of the originator product, Metacam 5 mg/ml solution for injection for use in dogs and cats. Bioequivalence between Rheumocam 5 mg/ml solution for injection for dogs and cats and the reference product was demonstrated.

Benefit assessment

Direct therapeutic benefit

The active substance, meloxicam, is a well known non-steroidal anti-inflammatory drug in veterinary medicine. It has been included in other formulations of Rheumocam which have already been authorised (oral suspension for dogs and horses, chewable tablets for dogs, injectable solution for cattle, pigs and horses). The primary mode of action of meloxicam is inhibition of cyclo-oxygenase in the arachidonic acid inflammatory pathway. It is beneficial in the alleviation of inflammation and pain in both acute and chronic musculoskeletal disorders in a number of species, including cattle, pigs and horses. It is accepted that the product will have an acceptable safety profile in the target species when administered at the recommended treatment dose.

Additional benefits

Additional benefits may be considered to arise from the reduction in severity of inflammation and pain in the agreed indications.

Risk assessment

It is accepted that the product does not represent an unacceptable risk to users when used in accordance with label instructions.

The product is not expected to pose a risk for the environment when used as recommended.

Risk management or mitigation measures

Appropriate sentences are included in the SPC and product information to prevent risks for the target animal, the user and the environment.

Evaluation of the benefit risk balance

The product has been shown a positive benefit-risk balance overall. Since bioequivalence has been demonstrated between the test and reference product in both cats and dogs through appropriate studies it can be concluded that Rheumocam 5 mg/ml solution for injection in dogs and cats will be as efficacious and safe as the reference product.

Conclusion

The overall benefit risk balance is deemed positive.

Based on the original and complementary data presented, it is concluded that the quality, safety, and efficacy of Rheumocam 5 mg/ml solution for injection in dogs and cats were considered to be in accordance with the requirements of Directive 2001/82/EC, as amended.

Following authorisation by the Commission, periodic safety update reports for Rheumocam will be required at 6-monthly intervals for the first two years, yearly for the next two years and thereafter at 3-yearly intervals. This was considered necessary to ensure more frequent pharmacovigilance monitoring in view of the extension of the indications to a new target species (cats).