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Committee for Medicinal Products for Veterinary Use

CVMP Assessment Report for the extension of a community marketing authorisation for Rheumocam (EMEA/V/C/000121/X/010)

Scope: New strength (5 mg/ml)

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

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Introduction

An application for an extension of a Community marketing authorisation of Rheumocam was submitted to the European Medicines Agency (the Agency) on 1 February 2012 by Chanelle Pharmaceuticals Manufacturing Limited in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I thereof. Rheumocam is a generic product containing meloxicam as active substance.

Rheumocam was given a marketing authorisation by the Commission on 9 December 2011.

The Rheumocam product range comprises 1.5 mg/ml oral suspension for dogs, 1 and 2.5 mg/ml chewable tablets for dogs, 5 mg/ml solution for injection for dogs and cats, 15 mg/ml oral suspension for horses and 20 mg/ml injection for solution for cattle, pigs and horses.

This Rheumocam extension concerns a new strength meloxicam 5 mg/ml solution for injection for cattle and pigs. The reference product is Metacam 5 mg/ml solution for injection for cattle and pigs.

The target species are cattle and pigs. The route of administration of the new strength in cattle is intravenous and subcutaneous and intramuscular in pigs.

The indications for Rheumocam 5 mg/ml solution for injection for cattle and pigs are:

Cattle:

For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle.

For use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle.

Pigs:

For use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation.

For the relief of post operative pain associated with minor soft tissue such as castration.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant provided an updated description of the pharmacovigilance system which is very similar to the version previously provided and assessed. It is considered to fulfil the requirements of the current legislation of the European Union.

Manufacturing authorisations and inspection status

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

Part 2 - Quality

Composition

Rheumocam 5 mg/ml solution for injection for cattle and pigs contains 5 mg/ml of meloxicam as active ingredient and 159.8 mg/ml of ethanol (96%) as antimicrobial preservative. Further excipients are

meglumine, Macrogol 400, Poloxamer 188, glycine, disodium edetate, sodium hydroxide, hydrochloric acid and water for injections. Some changes compared to the composition of the reference product were made in regard of the excipients, namely that glycofurol is replaced by Macrogol 400, hydrochloric acid by sodium chloride and disodium edetate is added.

It is noted that the formulation of Rheumocam 5 mg/ml solution for injection in cattle and pigs is identical to the recently authorised product Rheumocam 5 mg/ml solution for injection for dogs and cats.

Container

The product is presented in type I clear glass vials, closed with a type I bromobutyl rubber stopper and an aluminium cap. Pack sizes are 20 ml, 50 ml and 100 ml.

Development pharmaceutics

Rheumocam 5 mg/ml solution for injection for cattle and pigs has been formulated to closely resemble the reference product. The differences are described above.

Method of manufacture

The typical batch size may vary from 50 l to 2500 l. The manufacturing process consists of mixing ingredients, adjusting the 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 and filling of the vials. The description of the manufacturing process and the proposed in-process controls are satisfactory.

The validation of the manufacturing process has been conducted on two industrial-size batches of 500 l. The manufacturing process of the finished product Rheumocam 5 mg/ml solution for injection was 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 are submitted in an Active Substance Master File which has been assessed for the initial Rheumocam application.

Excipients

All of the excipients are described in the Ph. Eur. and fulfil the specifications according to their corresponding monograph.

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 for 6 months at 40 °C/75% RH are available. No relevant changes were observed. The proposed re-test period is considered acceptable.

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

The photostability study shows a slight degradation of the finished product for vials directly exposed to light. However the absence of the precaution "Keep vial in the outer carton" in section 6.4 of the SPC is accepted since the increase of the impurities during the photostability study is low and the content of these impurities in the finished product remain within the specifications.

The proposed in-use shelf-life of 28 days is accepted. Repeated in-use stability tests on batches of the finished product at the end of its shelf-life confirm the in-use 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. The reference product is Metacam 5 mg/ml solution for cattle and pigs.

Rheumocam 5 mg/ml solution for injection is considered bioequivalent with the reference product (see part 4 of this report). Therefore, pharmacodynamics, pharmacokinetics and the toxicological profile of the active substance meloxicam do not need to be reassessed. It can be concluded that the safety profile of Rheumocam 5 mg/ml solution for injection for cattle and pigs will be the same as for the reference product.

All excipients are commonly used in human and veterinary medicinal products and their toxicological profiles are well known. Therefore, it can be assumed that they will not raise a toxicological concern for the safety of the consumer, the user, target animals and for the environment.

User safety

The applicant has provided a user risk assessment that was conducted in accordance with the guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1).

All excipients included in the formulation of Rheumocam 5 mg/ml solution for injection are considered not to be of toxicological concern. The indications, the dosage and posology of the new strength are identical to those of the reference product and the product is considered bioequivalent with the reference product, as described above.

Therefore, it is accepted that the safety of Rheumocam 5 mg/ml to the user is the same as for the reference product and the same user safety statements are included in the SPC.

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 the treatment of an individual or a small number of animals in a flock or herd under veterinary prescription,

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.

Overall conclusions on the safety documentation

Rheumocam 5 mg/ml solution for injection for cattle and pigs is considered bioequivalent with the reference product even though no *in vivo* bioequivalence study was provided. The biowaiver is considered acceptable as a satisfactory justification was provided. Therefore, it can be concluded that the safety profile of Rheumocam 5 mg/ml solution for injection for cattle and pigs will be the same as for the reference product.

As all excipients are commonly used in human and veterinary medicinal products and their toxicological profiles are well known, it can be assumed that they will not raise a toxicological concern. The same warning sentences for the user as for the reference product will be included in the SPC which are adequate 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.

Residues documentation

In support of the application the applicant provided residue depletion studies with Rheumocam 20 mg/ml solution for injection presentation. The only difference between the test formulation and Rheumocam 5 mg/ml is the amount of the active substance and meglumine. This is considered acceptable as the test formulation has the higher quantity of meloxicam and meglumine compared to the 5 mg/ml strength.

Residue studies

No new studies have been provided. See below.

Pharmacokinetics

No studies on pharmacokinetics were performed with Rheumocam 5 mg/ml solution for injection for cattle and pigs as Rheumocam 5 mg/ml was considered bioequivalent with the reference product.

Depletion of residues

This application is made in accordance with Article 13.1(a)(iii) of Directive 2001/82/EC, as amended (a generic). As the product was considered bioequivalent with the reference product, a full depletion study with Rheumocam 5 mg/ml is considered not necessary but a confirmation study on depletion of the marker residue from the injection site.

Two GLP residue depletion studies were provided using the 20 mg/ml presentation which is considered acceptable instead of new confirmatory studies to conclude on the withdrawal periods. These studies were provided and assessed in a previous application for the determination of the injection site residue depletion profile of the product Rheumocam 20 mg/ml solution for injection for cattle, pigs and horses. The product was administered once subcutaneously in cattle at the recommended dose of 0.5 mg/kg bw and in pigs once intramuscularily at the recommended dose of 0.4 mg/kg bw.

In cattle injection side residue levels of meloxicam were below the Lower Limit of Quantification of the analytical method (5.0 µg/kg) from day 13 on; in pigs the residue levels were below the Limit of Detection (1.0 µg/kg) from day 4 on.

MRLs

The active substance in Rheumocam, meloxicam, is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissues	Other provisions	Therapeutic classification
Meloxicam	Meloxicam	Bovine, caprine, porcine, rabbit, *Equidae*	20 µg/kg 60 µg/kg 65 µg/kg	Muscle Liver Kidney	NO ENTRY	Anti-inflammatory agents/ Nonsteroidal anti-inflammatory agents
	Meloxicam	Bovine, caprine	15 µg/kg	Milk		

The excipients listed in section 6.1 of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Withdrawal periods

Given that bioequivalence was considered between Rheumocam 5 mg/ml and the reference product the withdrawal periods of the new product are the same as those of the reference product.

Additionally, the residue depletion studies performed with Rheumocam 20 mg/ml are acceptable to further justify the application of the withdrawal periods of the reference product as they are the same as for the 20 mg/ml strength.

Overall conclusions on the residues documentation

The established withdrawal periods of the reference product as listed below are applied to Rheumocam 5 mg/ml solution for injection for cattle and pigs.

Cattle:

Meat and offal: 15 days

Pigs:

Meat and offal: 5 days

As the target species are calves and young cattle only, no withdrawal period for milk is indicated.

Part 4 – Efficacy

This is an application for an extension to include a solution for injection for cattle and pigs containing 5 mg/ml meloxicam as active substance. The applicant claimed essential similarity to the reference product Metacam 5 mg/ml solution for injection even though the excipients of both formulations are not fully identical.

The SPC is in line with the SPC of the reference product.

No *in vivo* bioequivalence study was provided. In order to justify that the differences in the excipients have no influence on the rate and/or extent of absorption of meloxicam, the applicant has carried out additional *in vitro* studies on physico-chemical properties with Rheumocam 5 mg/ml. The data presented demonstrate that the differences in the formulations have no effect on the key physicochemical properties which could influence the absorption of the active substance, namely osmolality, viscosity, density and pH.

Therefore, the waiver of bioequivalence studies in cattle and pigs is acceptable according to point 7.1(b) of the bioequivalence guideline (EMA/CVMP/016/00-Rev.2) as if it was adequately justified that the difference in the excipients has no influence on the rate and/or extent of absorption of the active substance.

Rheumocam 5 mg/ml is considered bioequivalent with the reference product.

No tolerance data have been conducted with the product. Reported data came from studies conducted with the Rheumocam 20 mg/ml presentation. However, given that:

- the difference in composition of excipients with Metacam 5 mg/ml should not have impact on the absorption of the product,
- the toxicological profile of the active substance is well known and has been adequately characterised in the published literature, and
- the excipients are recognised as not of toxicological concern,

in view of provided additional studies that showed that the differences in the excipients have no influence on the rate and/or extent of absorption of meloxicam, the absence of tolerance studies that are specific to Rheumocam 5 mg/ml solution for injection for all target species can be supported.

Some published literature was provided to outline the pharmacodynamic and pharmacokinetic properties of the active substance, meloxicam.

As this is a generic application and given that the new product is considered bioequivalent with the reference product, there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

Hence, it is accepted that the efficacy profile and the clinical tolerance of the test and reference product are the same. As the differences in the excipients of the 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.

Part 5 – Benefit risk assessment

Introduction

The application for Rheumocam 5 mg/ml solution for injection for cattle and pigs is an extension of an existing generic veterinary medicinal product. The active ingredient is meloxicam. The product was developed in such a way as to closely resemble the formulation of the reference product, Metacam 5 mg/ml solution for injection for cattle and pigs. Rheumocam 5 mg/ml is considered bioequivalent with the reference product as it was shown that the differences in the formulations do not alter the absorption of the active substance.

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 authorised formulations of Rheumocam (oral suspension for dogs and horses, chewable tablets for dogs, injectable solution for cattle, pigs, horses, dogs and cats). The primary mode of action of meloxicam is inhibition of cyclo-oxygenases 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 such as dogs, cats, cattle, pigs and horses.

Additional benefits

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

Risk assessment

All excipients used in the formulation for Rheumocam 5 mg/ml solution for injection for cattle and pigs are commonly used in human and veterinary medicinal products and their toxicological profiles are well known. 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.

The risks identified are strictly the same as those that exist for the reference product Metacam 5 mg/ml solution for injection for cattle and pigs. The excipients do not pose any additional risks.

No residue depletion studies were provided with the 5 mg/ml strength which is acceptable. The available residue depletion studies with the authorised 20 mg/ml strength allow retaining the withdrawal period of the reference product for Rheumocam in both target species cattle and pigs (meat and offal). As the target species of Rheumocam 5 mg/ml formulation are calves and young cattle only, no withdrawal period for milk is indicated.

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

Risk management or mitigation measures

Appropriate sentences, as for the authorised reference product, are included in the SPC and product information to prevent risks for the user and for the environment.

Evaluation of the benefit risk balance

The product has been shown to have a positive benefit-risk balance overall. Although no *in vivo* bioequivalence study was provided the new product is considered bioequivalent with reference product. Rheumocam 5 mg/ml solution for injection in cattle and pigs is expected to have the same safety and efficacy profile as the reference product.

It is accepted that the withdrawal periods for meat and offal for cattle and pigs are the same as those established for the reference product; no withdrawal period for milk is indicated.

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 cattle and pigs were considered to be in accordance with the requirements of Directive 2001/82/EC, as amended.