5 May 2011
EMA/170257/2011
Veterinary Medicines and Product Data Management

Scientific Discussion post-authorisation update for Rheumocam extension X/007

Scope of extension: addition of 20 mg/ml solution for injection for cattle, pigs and horses

An application for an extension of the Community marketing authorisation for Rheumocam to include a 20 mg/ml solution for injection for cattle, pigs and horses was submitted to the European Medicines Agency on 29 June 2010 by Chanelle Pharmaceuticals Manufacturing Limited in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I thereof.

Rheumocam 20 mg/ml solution for injection for cattle, pigs and horses contains meloxicam as active ingredient and is presented in a cardboard box containing colourless glass injection vials of 20 ml, 50 ml, 100 ml or 250 ml.

It is indicated in:

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.

For adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy.

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

For adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy.

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Horses:
For use in the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders.

For the relief of pain associated with equine colic.

The route of administration is:

Cattle: subcutaneous or intravenous injection

Pigs: intramuscular injection.

Horses: intravenous injection.

Part 1 - Administrative particulars

The description of Chanelle Pharmaceuticals Manufacturing Limited's pharmacovigilance system fulfils the current legal requirements. Relevant details were provided on the manufacturing sites.

Part 2 - Quality

Composition

Rheumocam 20 mg/ml solution for injection contains 20 mg/ml of meloxicam as active ingredient and ethanol as an antimicrobial preservative.

Container

Rheumocam 20 mg/ml solution for injection for cattle, pigs and horses 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, 100 ml and 250 ml.

Development pharmaceutics

Rheumocam 20 mg/ml solution for injection for cattle, pigs and horses has been formulated to be "bioequivalent" to the reference product Metacam 20 mg/ml solution for injection for cattle, pigs and horses. No bioequivalence studies were presented.

Method of manufacture

Details on the typical batch size were provided as well as a description of the various steps of the manufacturing process. The description of the manufacturing process and the proposed in-process controls are satisfactory.

According to the provided data on validation, the manufacturing process of the finished product Rheumocam 20 mg/ml solution for injection for cattle, pigs and horses is considered validated.

Control of starting materials

Active substance

The active substance, meloxicam is described in the European Pharmacopoeia (Ph. Eur.). Data for meloxicam were submitted in an Active Substance Master File which has been assessed for previous applications for Rheumocam oral suspension for horses and dogs and Rheumocam chewable tablets for dogs.

Excipients

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

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

No input 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).

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 limit for degradation products in the shelf-life specification comply with the VICH guidelines.

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 were presented and comply with the required specification.

Stability

The proposed retest period for the active substance was described and considered acceptable. Results from storage of batches of the substance for up to 60 months at 25 °C/ 60% RH[1], at 30 °C/ 70% RH and for 6 months at 40 °C/ 75% RH are available. No relevant changes were observed. The proposed retest period was considered acceptable.

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

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 slight, and the content of these impurities in the finished product remain within the specification.

The proposed in-use shelf-life of 28 days is accepted.

[1] Relative humidity

Part 3 – Safety

As this application is made in accordance with Article 13.1(a) (iii) of Directive 2001/82/EC, as amended (i.e. a generic product), the toxicological profile of meloxicam does not need to be reassessed.

The excipients used in the formulation are well established and have an extensive history of use in injectable preparations at concentrations comparable to those specified for Rheumocam (apart from Macrogol 400 instead of Macrogol 300).

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

Based on the view that the limited difference in formulation compared to Metacam 20 mg/ml solution for injection for cattle, pigs and horses 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 Metacam 20 mg/ml solution for injection for cattle, pigs and horses, it can be accepted that the potential hazard to the user posed by Rheumocam 20 mg/ml solution for injection for cattle, pigs and horses will not be any greater than that posed by the reference product Metacam. The proposed user safety statements are considered appropriate.

The product is for individual treatment under veterinary prescription, and is extensively metabolised prior to excretion mainly in the faeces which, in the horse, is of minimal environmental relevance. Based on the Phase I decision tree, as the product is intended for the treatment of individual animals, the environmental risk assessment can end at Phase I. When used as recommended, the product will have a negligible impact on the environment.

Confirmatory GLP studies were performed with the recommended dosages for the determination of the injection site residue depletion profile of the new product Rheumocam 20 mg/ml solution for injection. Based on the data provided it was concluded that the withdrawal periods for meat, offal and cattle milk should be the same as for Metacam 20 mg/ml solution for injection. The product is not authorised for use in horses producing milk for human consumption.

Part 4 – Efficacy

The application for a marketing authorisation for Rheumocam is made in accordance with Article 13(1) of Directive 2001/82/EC (as amended), a generic application.

No bioequivalence studies have been performed. The only difference in formulation between Rheumocam 20 mg/ml solution for injection and the reference product Metacam 20 mg/ml solution for injection is the use of Macrogol 400 instead of Macrogol 300. The applicant conducted a comparative viscosity study and no significant difference was demonstrated between the two formulations. Hence, the difference in Macrogol is not expected to impact absorption of the product and exemption from conducting a bioequivalence study can therefore be accepted. The product contains the same active substance in the same concentration, has the same pharmaceutical form, and can be considered bioequivalent to the authorised reference product Metacam 20 mg/ml solution for injection for use in cattle, pigs and horses.

Part 5 – Benefit risk assessment

The application for Rheumocam 20 mg/ml solution for injection for cattle, pigs and horses is a generic application. The product was developed in such a way as to closely resemble the formulation of the originator product, Metacam 20 mg/ml solution for injection for use in cattle, pigs and horses.

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). The primary mode of action of meloxicam is inhibition of cyclooxygenases 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 or the environment when used in accordance with label instructions.

Risk management or mitigation measures

Appropriate sentences 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 only difference in formulation between Rheumocam 20 mg/ml solution for injection and the reference product Metacam 20 mg/ml solution for injection is the use of the diluent Macrogol 400 instead of Macrogol 300, which is proven to have no effect on viscosity of the product. The withdrawal periods for meat/ offals and milk, where appropriate, should be same as for Metacam 20 mg/ml solution for injection, and an exemption from conducting a bioequivalence study *in vivo* is deemed appropriate.

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 20 mg/ml solution for injection for cattle, pigs and horses were considered to be in accordance with the requirements of Directive 2001/82/EC, as amended.