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Committee for Medicinal Products for Veterinary Use

CVMP assessment report for the extension of a community marketing authorisation for Inflacam (EMEA/V/C/2497/X/002)

Scope: New strength and new target species (cats)

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 Inflacam 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. Inflacam is a generic product containing meloxicam as an active ingredient.

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

The Inflacam product range comprises 1.5 mg/ml oral suspension for dogs, 1 and 2.5 mg/ml chewable tablets for dogs, 15 mg/ml oral suspension for horses as well as a 20 mg/ml injection for solution for cattle, pigs and horses.

This Inflacam extension concerns a new strength meloxicam 5 mg/ml solution for injection for dogs and cats (cats also being a new target species) and represented 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 as well as the reduction of post-operative pain and inflammation following orthopaedic and soft tissue surgery; 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.

This application is a duplicate application to Rheumocam 5 mg/mg solution for injection in dogs and cats.

The CVMP adopted an opinion and CVMP assessment report on 14 June 2012.

On 16 August 2012, the European Commission adopted a Commission Decision for this application.

Part 1 – Administrative particulars

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

Detailed description of the pharmacovigilance system

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

Part 2 – Quality

Composition

Inflacam 5 mg/ml solution for injection contains 5 mg/ml of meloxicam as active ingredient and 159.8 mg/ml of ethanol (96 per cent) as antimicrobial preservative. Some changes compared with the composition of the reference product were made in regard to the excipients; namely, glycofurol is replaced by Macrogol 400, hydrochloric acid by sodium chloride and disodium edetate is present additionally.

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

Inflacam 5 mg/ml solution for injection in dogs and cats has been formulated to resemble closely the reference product Metacam 5 mg/ml solution for injection in dogs and cats.

Method of manufacture

The typical batch size may vary from 250 litres to 2500 litres. The manufacturing process consists of 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 in 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 controls are satisfactory. The validation of the manufacturing process has been conducted on two industrial batches of 500 litres. The manufacturing process of the finished product Inflacam 5 mg/ml 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 have been submitted in an Active Substance Master File which has been assessed for the initial Inflacam application.

Excipients

All the excipients are described in the Ph. Eur. and 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 are 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 (e.g. at product-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 five 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 six months at 40 °C/75% RH are available. No relevant changes were observed. The proposed retest period is considered acceptable.

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

A 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 test on a batch of the finished product approaching the end of its shelf-life. The results will be available end of June/July 2012.

Overall conclusions on quality

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

Part 3 – Safety

Safety documentation

Although the list of excipients for Inflacam 5 mg/ml solution for injection in dogs and cats is not identical to those of the reference product Metacam, all of them are used commonly 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 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 Inflacam 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 Inflacam 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.

As a new target species (cats) will be added to the product range, it was considered whether to re-set the PSUR cycle. However, as the product has only recently been authorised (December 2011) and may not have been placed on the market yet, a re-setting of the PSUR cycle was not considered necessary.

Pharmacodynamics

See Part 4.

Pharmacokinetics

See Part 4.

User safety

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

Given that the limited difference of formulation with Metacam 5 mg/ml solution for injection in 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, then it can be accepted that the potential hazard to the user posed by Inflacam 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 product.

Overall conclusions on the safety documentation

Bioequivalence with the reference product has been established for dogs and cats. It can be concluded that the safety of Inflacam 5 mg/ml solution for injection in dogs and cats will be the same as for the reference product.

All excipients are used commonly 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. The same warning sentences for the user as for the reference product are included in the SPC, which are adequate to ensure the safety of the person whom 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 is 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 bioequivalence to the reference product was shown, sections 5.1 and 4.2 of the SPC are identical to those of 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, the no specific tolerance studies are required, in order to determine margins of safety in the target species.

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

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

The bioequivalence between the two products Inflacam and Metacam was also demonstrated in cats.

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

Overall conclusion on efficacy

Given 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

Introduction

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

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 Inflacam 5 mg/ml solution for injection in dogs and cats are used commonly 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.

It is considered 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 as well as teh product information to prevent risks for the target animals, the user and the environment.

Evaluation of the benefit risk balance

The product has been shown to have 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, then it can be concluded that Inflacam 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 Inflacam 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.