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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment for the granting of a community marketing authorisation for Inflacam (EMEA/V/C/002497)

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

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Introduction

An application for the granting of a community marketing authorisation of Inflacam has been submitted to the Agency on 1 June 2011 by Chanelle Pharmaceuticals Manufacturing Limited in accordance with Regulation (EC) No. 726/2004. This application is a duplicate application to Rheumocam for the following pharmaceutical forms and strengths: Rheumocam 1.5 mg/ml oral suspension for dogs, Rheumocam 1 mg and 2.5 mg chewable tablets for dogs, Rheumocam 15 mg/ml oral suspension for horses, and Rheumocam 20 mg/ml solution for injection for cattle, pigs and horses. The product was eligible for the centralised procedure under Article 3(3) of Regulation (EC) No. 726/2004 as it is a generic medicinal product of a reference medicinal product, Metacam, authorised by the Community.

Inflacam contains meloxicam and is presented in packs/containers of:

15, 42, 100, and 200 ml bottles for the oral suspension for use in dogs;

20 or 100 tablets (2 or 10 times 10 tablet blisters) for the chewable tablets for use in dogs;

100 and 250 ml bottles of oral suspension for use in horses;

20, 50, 100, and 250 ml vials for the solution for injection in cattle, pigs and horses.

Inflacam is indicated for alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders. The route of administration is oral use for the oral suspension and tablets and subcutaneous use for the solution for injection. The target species are dogs, horses, cattle and pigs.

Part 1 - Administrative particulars

The applicant has provided a detailed description of the pharmacovigilance system (DDPS). The information provided demonstrate that the applicant has in place a pharmacovigilance system that will allow it to comply with the legal requirements in respect of pharmacovigilance.

GMP certificate and manufacturing authorisation are respectively dated March and April 2011. No inspection is requested.

The submitted studies are those previously assessed and there are no new data.

Part 2 - Quality

Composition

1.5 mg/ml oral suspension for dogs

Inflacam oral suspension for dogs contains 1.5 mg/ml meloxicam as active substance. Conventional pharmaceutical excipients are used (saccharin sodium, sodium carboxyl methyl cellulose, colloidal silicon dioxide, citric acid monohydrate, sorbitol sodium, disodium hydrogen phosphate dodecahydrate, sodium benzoate and honey flavour). The primary packaging materials consist of a white polyethylene terephthalate (PET) bottle for the 42 ml, 100 ml and 200 ml pack sizes and a high density polyethylene (HDPE) bottle for the 15 ml pack size with a polypropylene measuring syringe and tamper proof child resistant closure.

1 and 2.5 mg/ml chewable tablets for dogs

Inflacam chewable tablets contain 1 mg and 2.5 mg meloxicam respectively as active substance and the excipients lactose monohydrate, silicified microcrystalline cellulose, sodium acid citrate, crospovidone, talc, pork flavour and magnesium stearate. The tablets are packed in blister packs made up of a PVC/PVDC with a 20 µm foil (aluminium foil). Pack sizes are of 20 and 100 tablets.

15 mg/ml oral suspension for horses

Inflacam 15 mg/ml oral suspension for horses contains 15 mg/ml of meloxicam as active ingredient. The excipients present in the formulation are saccharin sodium, carmellose sodium, silica colloidal anhydrous, citric acid monohydrate, sorbitol, disodium phosphate dodecahydrate as well as a preservative (sodium benzoate) and a honey flavour.

20 mg/ml injection for solution for cattle, pigs and horses

Inflacam 20 mg/ml solution for injection contains 20 mg/ml of meloxicam as active ingredient and the excipients ethanol as an antimicrobial preservative, poloxamer 188, macrogol 400, glycine, disodium edetate, sodium hydroxide, hydrochloric acid and meglumine.

Development pharmaceutics

1.5 mg/ml oral suspension for dogs

Inflacam oral suspension has been formulated to be essentially similar to the reference product, Metacam oral suspension 1.5 mg/ml, and contains the same active ingredient, meloxicam, used in the reference product. Inflacam oral suspension has comparable physical characteristics to the reference Metacam product, i.e. viscosity and pH.

Meloxicam is a stable substance and no interactions with the excipients have been observed. The excipients used in this formulation are well known and commonly used in the pharmaceutical and food industry. Sodium carboxymethyl cellulose and colloidal silicon dioxide are widely used as suspending agents in oral suspensions. The pharmacokinetics of the test product, Inflacam Oral Suspension and the reference product, Metacam Oral Suspension, were compared in the target species dogs, by way of a bioequivalence study. The results of the bioequivalence study show that the products are bioequivalent within normal confidence limits established in the guideline (EMEA/CVMP/016/00) for the Conduct of the Bioequivalence Study for Veterinary Medicinal Products.

Sodium benzoate has been chosen as a suitable preservative as it is effective against bacteria and moulds in low concentration, has low toxicity, and is stable and active over a wide range of pH and temperatures. Sodium benzoate is also used as the preservative in the reference product Metacam 1.5 mg/ml. Preservative efficacy testing was performed at the initial time point for the stability batches and the results conformed to the European Pharmacopoeia (Ph. Eur.) acceptance criteria A. 5.1.3.

As sweeteners sorbitol solution and sodium saccharin have been chosen as they are widely used in suspensions. Disodium hydrogen phosphate dodecahydrate and citric acid monohydrate have been chosen as buffering agents. The levels have been chosen to give a pH value similar to that of Metacam 1.5 mg/ml.

Inflacam 1.5 mg/ml oral suspension is packed in PET bottles for the 42 ml, 100 ml and 200 ml pack sizes and a HDPE bottle for the 15 ml pack size with a polypropylene measuring syringe and a polyethylene tamper proof child resistant closure. The suitability of the primary packaging was investigated as part of the stability studies performed.

1 and 2.5 mg/ml chewable tablets for dogs

For Inflacam chewable tablets the formulation has been developed to be bioequivalent to the reference product Metacam tablets and contains the same active ingredient used in the reference product. Meloxicam, the active ingredient, is purchased to Ph. Eur. specification with a Certificate of Analysis detailing the tests conducted by the manufacturer. Each of the excipients with the exception of the flavouring agent is purchased to Ph. Eur. specifications. The properties of the excipients are well known and are used frequently in the solid dosage forms. The only exception in this case is flavouring, i.e. Pork Flavour Givaudan which conforms to the supplier's internal standards.

15 mg/ml oral suspension for horses

Inflacam 15 mg/ml oral suspension for horses has been formulated to be bioequivalent to the reference product Metacam 15 mg/ml oral suspension for horses.

The anti-microbial preservative efficacy testing has been performed according to the European Pharmacopoeia (Ph. Eur.) and shows a satisfactory antimicrobial efficacy of the sodium benzoate in the finished product at the low limit.

20 mg/ml injection for solution for cattle, pigs and horses

Inflacam 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

1.5 mg/ml oral suspension for dogs

The proposed batch sizes range for the manufacture of Inflacam 1.5 mg/ml oral suspension were defined and the manufacturing formula for the standard batch size was provided. For larger batch sizes, quantities and volumes are scaled up accordingly.

A flow diagram of the manufacturing process for the standard batch size was provided and details of the in-process controls performed were also provided. The manufacturing process and in-process controls are described appropriately and are considered adequate.

A validation study has been performed on the first full scale manufacturing batches produced in stainless steel tanks. All results were within the acceptance criteria set up in the validation report.

1 and 2.5 mg/ml chewable tablets for dogs

The proposed commercial batch sizes range for the manufacture of Inflacam 1 mg and 2.5 mg tablets were defined for each tablet strength and the manufacturing formula presented.

A flow diagram of the manufacturing process for the standard batch size was provided and details of the in-process controls performed were also provided. The manufacturing process and in-process controls are described appropriately and are considered adequate.

Validation reports for the tabletting mixture preparation (blend) and compressing procedure for a number of batches for 1 mg and 2.5 mg Inflacam tablets were presented. Data from validation studies confirmed that the manufacturing process for Inflacam tablets (2.5 mg and 1 mg) using materials of the stated quality and the equipment specified is a suitable one and will consistently yield the product of the desired quality as described in the Finished Product Specifications.

15 mg/ml oral suspension for horses

The finished product is manufactured according to a standard process in which the in-process controls guarantee the reproducibility of the manufacture. The validation of the manufacturing process has been satisfactorily demonstrated.

20 mg/ml injection for solution for cattle, pigs and horses

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 Inflacam 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 Ph. Eur.. Data for meloxicam were submitted in an Active Substance Master File which has been assessed previously.

The assay of meloxicam is by non-aqueous titration and related substances are determined by the validated methods described. Additional in-house methods were also described and these methods have been validated.

Meloxicam exists in 5 polymorphic forms I, II, III, IV and V. These forms can be differentiated on the basis of their infrared absorption spectra and X-ray diffraction pattern. The active substance supplier routinely manufactures polymorphic form I for supply to the applicant for the manufacture of meloxicam liquid. Particle size was limited on the active substance specification.

Residual solvents used in the manufacturing process of meloxicam were listed, and their quantity is controlled according to specifications in line with EU/VICH limits.

Satisfactory data on batch results were presented and all results were within the relevant specifications.

Excipients

1.5 mg/ml oral suspension for dogs

All excipients are tested according to their corresponding monographs except for honey flavour, which is tested according to the supplier's specifications. The relevant certificates of analysis issued by the suppliers have been provided. All excipients comply with their respective monographs and typical certificates of analysis demonstrating compliance for each are provided.

Honey flavour is not described in a pharmacopoeia. The certificate of analysis issued by the supplier and details of the in-house tests and specifications have been provided. The main constituent of honey flavour is a well-established pharmaceutical formulation excipient. The technical data sheet for honey flavour also states that this excipient is recommended for general pharmaceutical applications. The stability data provided demonstrate that the excipient honey flavour is compatible with both the active ingredient meloxicam and with the other excipients present in Inflacam 1.5 mg/ml Oral Suspension.

1 and 2.5 mg/ml chewable tablets for dogs

All excipients are tested according to their corresponding monographs except for Pork Flavour, which is tested according to the supplier's specifications. The relevant certificates of analysis issued by the suppliers have been provided.

Pork Flavour is not described in a pharmacopoeia. The relevant certificate of analysis issued by the supplier has been provided.

15 mg/ml oral suspension for horses

The excipients are described in the Ph.Eur. except the honey flavour for which supplier's data are provided.

20 mg/ml injection for solution for cattle, pigs and horses

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

Packaging Material

1.5 mg/ml oral suspension for dogs

The primary packaging materials consist of a white PET bottle (for the 42 ml, 100 ml and 200 ml pack sizes) closed with a child proof tamper evident high density polyethylene cap. The temper evident ring is high density polyethylene coloured to the yellow colour, the input of the cap is made from low density polyethylene. A declaration from the supplier certifying that the PET resins comply with the Ph. Eur. monograph 3.1.15 ("Polyethylene terephthalate for containers for preparations not for parental use"), and specifications for tamper evident lids (used in the initial stability studies and stability studies) were provided. The primary packaging material for the 15 ml pack size is an HDPE bottle. Stability studies performed in the final packaging have been addressed and no incompatibilities between the immediate packaging and suspension have been found.

1 and 2.5 mg/ml chewable tablets for dogs

The primary packaging material consists of PVC/PVDC with a 20 µm aluminium foil. Certificates from the manufacturers were provided. Some routine tests for foils of blisters include: correct dimension, appearance, correct code number, correct grade material, pin hole test, heat sealing, IR identification. Stability studies performed in the final packaging show that no incompatibilities between the immediate packaging and tablets have been found.

15 mg/ml oral suspension for horses

The product is presented in HDPE bottles of 100 and 250 ml with a measuring syringe. The applicant has demonstrated that a reproducible and accurate dose of the product is delivered with the measuring syringe under testing conditions which take due account of the range of the proposed dosage regimen.

Inflacam 20 mg/ml solution for injection for cattle, pigs and horses

The product is presented in type I clear glass vials, closed with a type I bromobutyl rubber stopper and an aluminium cap.

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

Declarations were provided from all manufacturers of the starting materials that 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-Rev.2).

Control tests on the finished product

1.5 mg/ml oral suspension for dogs

The finished product release and shelf life specifications were provided. The methods used for identification and assay of meloxicam and to determine sodium benzoate were provided. The methods have been fully validated and the validation reports were provided.

1 and 2.5 mg/ml chewable tablets for dogs

The specification complies in general with VICH requirements and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances and meets the requirements of the general method of the European Pharmacopoeia for "Tablets" (Dosage Forms). Methods used for identification and assay of meloxicam were described. Details for the meloxicam quantification during the dissolution tests of Inflacam Tablets (1 mg and 2.5 mg strength) have also been provided.

Assay validation for content of meloxicam in Inflacam tablets was detailed. The assay was validated according to current VICH requirements; validation of analytical procedures. The parameters evaluated during the validation of the assay with the acceptance criteria were described. The assay for determination of the concentration of meloxicam after dissolution of Inflacam tablets has been described and validated. The assay was validated according to current VICH requirements: Validation of analytical procedures.

Batch analyses of production batches for both the oral suspension and chewable tablets manufactured at Chanelle Pharmaceuticals Manufacturing Ltd., Ireland were presented. The results conformed to the relevant specifications.

15 mg/ml oral suspension for horses

The in-process controls described in the dossier are satisfactory. The release specifications of the finished product are considered acceptable for this type of dosage form. The control methods used in the control of the finished product at release are well validated.

20 mg/ml injection for solution for cattle, pigs and horses

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

1.5 mg/ml oral suspension for dogs

Stability tests on the active substance(s)

The following re-test period/storage condition was proposed: 24 months / no special requirements for storage. The stability data support 2 years with no special storage conditions. Stability studies have been carried out on batches at 25°C/ RH 60% up to 24 months and at accelerated conditions 40 °C/ RH 75% for 6 months. All relevant parameters of the specification were investigated.

Stability tests on the finished product

A description was provided of relevant stability studies performed. Stability data from batches of finished product in the package not intended for marketing (white polyethylene bottles with a tamper evident polyethylene cap) were available. The batches were stored for 24 months at 25°C/60% RH and 6 months at 40°C/75% RH. No significant changes at both conditions were observed. The results remained within specification limits. The data supported the absence of a storage precaution for the product and a shelf-life of 2 years with no specific precaution for storage was considered acceptable.

In-use stability tests

Stability results were presented for batches stored at 25°C 60% RH for 24 months and for batches at 40°C 75% RH for 6 months. These stability results indicate that the product stored in a semi-permeable container can withstand low relative humidity environments.

1 and 2.5 mg/ml chewable tablets for dogs

Stability tests on the active substance(s)

Details on the stability of the raw material, meloxicam, were provided.

Stability tests on the finished product

Stability data from a number of batches of finished product in the package were presented, having been stored for 6 months at 40°C/ 75% RH and 12 months at 25°C/ 60% RH. Observed parameters were within specification limits.

A shelf-life of 3 years is considered acceptable in the light of the long term stability studies on the finished product that have been provided.

In-use stability tests

No data were provided. As the active substance has been shown to be stable and this also is the case for the finished product when stored in blister packs, it is considered acceptable not to perform in-use stability testing.

15 mg/ml oral suspension for horses

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% relative humidity, at 30°C/ 70% RH and for 6 months at 40°C/ 75% RH are available. No relevant changes were observed.

Results from storage of the finished product were also presented. Batches have been stored for 18 months at 25°C/ 60% RH and for 6 months at 40°C/ 75% RH. Based on the current results, the proposed shelf-life of 36 months is accepted.

The applicant has provided an in-use stability study at 3 months. Based on the available results, the 3-month in-use shelf-life is accepted.

20 mg/ml injection for solution for cattle, pigs and horses

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% relative humidity, 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 the 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.

Overall conclusions on quality

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

Part 3 – Safety

As essential similarity to the reference product was confirmed, the results of toxicological and pharmacological tests and clinical trials were not required in accordance with Article 13 of Directive 2001/82/EC, as amended.

User risk assessment

1.5 mg/ml oral suspension for dogs

1 and 2.5 mg/ml chewable tablets for dogs

A satisfactory user safety assessment has been provided by the applicant.

Given that Inflacam is demonstrated to be bioequivalent to Metacam, the potential impact of the active substance in respect of user safety will be the same for both products. The excipients used in the formulation are well established and have an extensive history of use in oral preparations at concentrations comparable to those specified for Inflacam. 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 intended posology and indications are identical to those of the reference product, Metacam, therefore, the same exposure scenarios exist.

Risk management phrases as authorised for Metacam are included in the SPC and product literature.

Based on the fact that bioequivalence is demonstrated with Metacam (see part 4), that the excipients included in the formulations can be considered safe and that the posology and indications are identical to those of the reference product, it can be accepted that the potential hazard to the user posed by Inflacam will not be any greater than that posed by the reference product. The proposed user safety statements were considered appropriate.

15 mg/ml oral suspension for horses

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 fact that bioequivalence is claimed with Metacam oral suspension for horses, that the excipients included in the formulations are considered safe and that the posology and indications are identical to those of the reference product Metacam, it can be accepted that the potential hazard to the user posed by Inflacam oral suspension for horses will not be any greater than that posed by the reference product. The proposed user safety statements are considered appropriate.

The product is intended to be used in horses for the alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders.

20 mg/ml injection for solution for cattle, pigs and horses

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 Inflacam.

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 Inflacam 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.

Environmental risk assessment

1.5 mg/ml oral suspension for dogs

1 and 2.5 mg/ml chewable tablets for dogs

The product is intended to be used in dog, a companion animal, and because of this the environmental risk assessment stopped in Phase I.

15 mg/ml oral suspension for horses

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 and no further data on environmental risk assessment are deemed necessary.

20 mg/ml injection for solution for cattle, pigs and horses

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.

Overall conclusions on safety

Based on the information presented, it is accepted that the risk to the user will be identical to that posed by the reference product and that the user safety statements proposed for inclusion in the SPCs are appropriate.

It is accepted that the product, when used in accordance with label directions, will not pose an unacceptable risk to the environment.

Residues

15 mg/ml oral suspension for horses

This is a generic application for a product administered by the oral route. As bioequivalence is correctly demonstrated between the new product, Inflacam 15 mg/ml oral suspension for horses, and the reference product, Metacam 15 mg/ml oral suspension for horses, it is not necessary to perform residue depletion studies with the new product. The established withdrawal period of the reference product will be applied for the new product, i.e. 3 days. From a consumer safety perspective, all excipients were considered safe as used in the product.

In the SPC, in section 4.11, the following labelling has been added for the withdrawal period of milk "Not authorised for use in lactating animals producing milk for human consumption."

20 mg/ml injection for solution for cattle, pigs and horses

Confirmatory GLP studies were performed with the recommended dosages for the determination of the injection site residue depletion profile of the new product Inflacam 20 mg/ml solution for injection.

Given that 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, that is proven to have no effect on viscosity of the product, the results of the residue depletion studies are not considered to be pivotal and a justification can be made that the withdrawal periods for meat/ offals and milk should be the same as for Metacam 20 mg/ml, including in horses. The product is not authorised for use in horses producing milk for human consumption.

Overall conclusions on the residues documentation

It can be accepted that the withdrawal periods for Metacam 15 mg/ml oral suspension for horses and Metacam 20 mg/ml solution for injection for cattle, pigs and horses can be applied to the product Inflacam 15 mg/ml oral suspension for horses and Inflacam 20 mg/ml solution for injection for cattle, pigs and horses.

Part 4 – Efficacy

This application was presented in accordance with Article 13(1) of Directive 2001/82/EC as amended, which refers to applications for veterinary medicinal products which are generics of a reference medicinal product authorised within the Community. In accordance with this provision, Inflacam is a generic of Metacam.

The active substance is meloxicam, a non-steroidal anti-inflammatory drug belonging to the acidic enolcarboxamide (oxicam) class. *In vitro* meloxicam is preferentially active against cyclooxygenase-2.

As essential similarity to the reference product was confirmed, the results of toxicological and pharmacological tests and clinical trials were not required in accordance with Article 13(1) of Directive 2001/82/EC, as amended.

1.5 mg/ml oral suspension for dogs

The proposed indication for Inflacam 1.5 mg/ml Oral Suspension for Dogs is for the alleviation of inflamation and pain in both acute and chronic musculo-skeletal disorders.

The recommended posology consists of an initial single dose of 0.2 mg meloxicam/kg bw on the first day, followed by once daily administration (24-hour intervals) of 0.1 mg meloxicam/kg bw. The product is to be administered mixed with food, and measured using a measuring syringe as supplied with the product.

The reference and the test products have the same pharmaceutical form (oral suspension) and the reference and the test products have the same qualitative and quantitative composition in active substance: 1.5 mg/ml of meloxicam.

A study of bioequivalence *in vivo* was performed in dogs between the 2 formulations Inflacam and Metacam after a single oral administration. The study was designed to meet the requirements of the Guideline for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMEA/CVMP/016/00).

Fasting Beagle dogs were treated with a single oral administration of meloxicam. Food was given immediately after the treatment.

The protocol was a two period, two treatment, two sequence crossover design. Dogs were observed several times daily for appearance and behaviour, blood samples were stored at –20°C and the sampling times were pre-dose and at appropriate time intervals post-dose. The analytical method was appropriate and was validated in a GLP study.

The pharmacokinetic parameters of meloxicam following oral administration in dogs of meloxicam were studied and in the results of the bioequivalence analysis the confidence intervals for the parameters $AUC_{0\text{-infinity}}$ and C_{max} were within the acceptable range, therefore it was concluded that Inflacam was bioequivalent to the reference product Metacam when administered to dogs. Similarities in $T_{1/2\ elim}$ showed that there were no differences in kinetics between the two formulations.

The active substance, meloxicam, is present in Inflacam in the same concentration as in the reference product Metacam. In respect of active substance, a similar tolerance profile for both products can be assumed. Excipients present in the formulation of Inflacam are commonly used in veterinary medicines and food products and can be considered safe. In view of the above, it was concluded that the safety profile of Inflacam is comparable to Metacam and therefore the same warnings are included in the SPC and product literature.

The information relating to adverse effects, precautions for use, interactions and overdose included on the proposed SPC for Inflacam is similar to that included on the SPC of the reference product, Metacam.

1 and 2.5 mg/ml chewable tablets for dogs

Data were presented relating to a GLP study intended to demonstrate bioequivalence of Inflacam 2.5 mg chewable tablets for dogs with the authorised reference product Metacam 2.5 mg chewable tablets for dogs. The study was designed to meet the requirements of the Guideline for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMEA/CVMP/016/00).

The test and the reference products had the same pharmaceutical form: chewable tablet.

The test and reference products had the same qualitative and quantitative composition in terms of active substances: 1 or 2.5 mg of meloxicam per chewable tablet.

A GLP bioequivalence study was performed in dog following single oral administration of one tablet per animal with the products Metacam 2.5 mg chewable tablets for dogs and Inflacam 2.5 mg chewable tablets for dogs.

Based on the results of the in-life animal phase, the results of the meloxicam plasma analytical phase, the resulting derived pharmacokinetic parameters and their subsequent bioequivalence statistical analysis, it was concluded that Inflacam 2.5 mg chewable tablets for dogs is bioequivalent to the registered reference compound Metacam 2.5 mg chewable tablets for dogs.

The bioequivalence between the 2 products Metacam and Inflacam 2.5 mg chewable tablets for dogs was demonstrated for the main kinetic parameters: C_{max} and $AUC_{infinity}$ and with the additional parameter $T_{1/2\ terminal}$.

A comparative dissolution was performed between Metacam 2.5 mg chewable tablets for dogs and Inflacam 2.5 mg chewable tablets for dogs in phosphate buffer at pH 7.5 and 4.5 and in 0.1 M HCl.

Another comparative dissolution was performed between Inflacam 1 mg chewable tablets for dogs and Inflacam 2.5 mg chewable tablets for dogs, and between Metacam 1 mg chewable tablets for dogs and Inflacam 1 mg chewable tablets for dogs.

Since bioequivalence between Inflacam and the reference product has been shown, it is expected that the products in terms of efficacy and safety will behave in a very similar manner.

15 mg/ml oral suspension for horses

A GLP bioequivalence study was performed in horses between Metacam and Inflacam 15 mg/ml oral suspension for horses following single oral administration of meloxicam at 0.6 mg/kg bw. This study was correctly performed (design, target species, treatment). The analytical method used to assay meloxicam in plasma samples was correctly validated. From the data, the bioequivalence of two products is demonstrated, i.e. Inflacam 15 mg/ml oral suspension for horses is bioequivalent with Metacam 15 mg/ml oral suspension for horses. From this study, it was also shown that, at the claimed dose, the product is well tolerated. Section 5 of the SPC of Rheumocan 15 mg/ml oral suspension for horses is identical to the SPC of Metacam 15 mg/ml oral suspension for horses.

As bioequivalence has been demonstrated, the expected efficacy and tolerance profile in the field is the same as that of the reference product.

20 mg/ml injection for solution for cattle, pigs and horses

No bioequivalence studies were performed. The only difference in formulation between Inflacam 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 Inflacam (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 and 20 mg/ml solution for injection for cattle, pigs and horses) is a generic application. Furthermore, it is a duplicate application to Rheumocam. The product was developed in such a way as to closely resemble the formulations of the originator product, Metacam. Inflacam is indicated for alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders.

Benefit assessment

Direct therapeutic benefit

The active substance, meloxicam, is a well known non-steroidal anti-inflammatory drug in veterinary medicine. 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: dogs, 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.

Since bioequivalence was confirmed *in vivo* between the two products Inflacam and the reference product Metacam oral suspension in dogs, Inflacam is expected to be as safe and efficacious as Metacam oral suspension.

In line with the requirements for demonstration of bioequivalence, studies on bioequivalence were furnished which showed that the 2.5 mg tablets, the highest strength, were bioequivalent in the dog. Appropriate dissolution studies allowed to also conclude on bioequivalence for the 1 mg strength tablet.

Since bioequivalence was demonstrated *in vivo* between the two products, Inflacam 15 mg/ml oral suspension for horses is expected to be as safe and efficacious as Metacam 15 mg/ml oral suspension for horses.

Additional benefits

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

Inflacam 1 and 2.5 mg/ml chewable tablets for dogs is presented as chewable tablets with pork flavour for easy administration to dogs.

Inflacam 15 mg/ml oral suspension for horses is presented as an oral suspension with honey flavour for easy administration to horses.

Risk assessment

The excipients used in the formulation for 1.5 mg/ml oral suspension for dogs are well established and have an extensive history of use in oral preparations at concentrations comparable to those specified for Inflacam. 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 for the 1 and 2.5 mg/ml chewable tablets for dogs are strictly the same as those that exist for the reference product. The excipients do not pose any additional risks.

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, as authorised for Metacam, 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 Inflacam 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 the 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 data presented, it is concluded that the quality, safety, and efficacy of Inflacam 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.

Conclusion

It is concluded that the duplicate dossier Inflacam can be considered strictly identical to Rheumocam. Updates to the dossier have been made where appropriate. There are no outstanding recommendations for data to be submitted.

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Directive 2001/82/EC as amended.