EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 September 2011
EMA/534781/2010
Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment report
Recocam (EMEA/V/C/002247)

International non-proprietary name: meloxicam

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

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1. Summary of the dossier

On 14 July 2011, the Committee for Medicinal Products for Veterinary Use (CVMP) adopted a positive opinion,[1] recommending the granting of a marketing authorisation for the generic veterinary medicinal product Recocam, a meloxicam 20 mg/ml solution for injection, intended for administration to cattle, pigs and horses. The applicant for this veterinary medicinal product is CF Pharma Limited.

The application was submitted under Article 3(3) of Regulation (EC) No. 726/2004 in accordance with Article 13.1 of Directive 2001/82/EC as amended (a generic application).

The active substance of Recocam is meloxicam, an anti-inflammatory and anti-rheumatic medicinal product, non-steroids (oxicams) with ATCvet code: QM01AC06.

The benefits of Recocam are the alleviation of inflammation and relief of pain in he approved indications.

The approved indications are identical to those included in the SPC of the reference product, Metacam 20 mg/ml solution for injection for cattle, pigs and horses, namely:

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.

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 most common side effects to be expected are a slight transient swelling at the injection site following subcutaneous administration in cattle and intravenous administration in horses.

2. Quality assessment

Composition

Recocam is a generic medicinal product of a reference medicinal product Metacam 20 mg/ml solution for injection (Marketing Authorisation Holder Boehringer Ingelheim Vetmedica GmbH) as authorised by the Community. The product consists of the active substance meloxicam and the excipients ethanol, anhydrous citric acid, poloxamer 188, meglumine, glycine, macrogol 300, sodium hydroxide, hydrochloric acid and water for injections. Like the reference medicinal product, the proposed pharmaceutical form of Recocam is a solution for injection.

Container

The product is to be packaged in 10 ml, 50 ml and 100 ml clear Type I glass vials closed with bromobutyl bungs and aluminium caps.

[1] Applicants may appeal any CVMP opinion, provided they notify the European Medicines Agency in writing of their intention to appeal within 15 days of receipt of the opinion.

Development Pharmaceutics

The dossier includes an extensive pharmaceutical development section in which the components of the formulation are discussed. The applicant proposes to use the same excipients in the generic product as are used in the reference product with the exception of citric acid which will be used as the chelating agent.

The suitability of terminal sterilisation was investigated during development work. Arising from these studies, it has been demonstrated that the steam sterilisation process employed delivers an adequate and reproducible level of lethality when operating routinely (in accordance with Ph. Eur. 5.1.1 – Methods of preparation of sterile products) and validation data for the steam sterilisation cycle employed have been provided.

The proposed concentration of the preservative in the generic product is identical to that which is included in the reference product and hence can be accepted.

Method of manufacture

The manufacturing process is a simple standard process involving sequential addition and mixing of the excipients and active in water for injection. Process validation on three batches of the product is provided and is considered adequate by way of demonstrating that the manufacturing and filling process is validated.

Final sterilisation process is by way of heat sterilisation and full validation data for the process have been provided.

Control of starting materials

Active substance

The active substance meloxicam is supported by a Ph. Eur. Certificate of Suitability, and a specification for the active substance as applied by the dosage form manufacturer is provided. Ph. Eur. test methods are utilised for analysis and are referred to on the specification.

Excipients

Each of the excipients complies with the relevant Ph. Eur. Monograph.

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

None of the excipients used in the product are of human or animal origin. The raw materials and the finished product are compliant with the Note for Guidance for minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products EMEA/410/01 Rev. 2 October 2003.

Control tests during production

Not applicable.

Control tests on the finished product

The specifications proposed for use for release and shelf-life purposes are considered appropriate to control the quality of the finished product. The active substance, related substances and preservative are all controlled within appropriate limits. Test methods for the identification and quantitative determination of meloxicam and its related substances, determination of the preservative content, and test for sterility are all described and are accompanied by appropriate validation data.

Stability

Active substance

The stability data provided support the claimed re-test period.

Finished Product

Finished product stability data are presented for three batches of the finished product packaged as proposed for marketing. The batches were stored under long-term and accelerated conditions according to VICH guidelines.

The proposed 36 month shelf-life for the product was justified in accordance with the CVMP note for guidance on stability testing of existing active substance and related finished products (EMEA/CVMP/846/99). The data were considered acceptable to support the 36 months with no special storage conditions required.

In-Use Stability

An in-use stability study was performed on a recently manufactured batch of product packaged in 10 ml vials. The study was continued for 28 days. Data have been provided that support the stopper being broached 20 times and this is reflected in the product literature.

Photostability

Photostability studies on a single batch of the product show that no photo-degradation of the active substance takes place. The clear glass packaging is considered to be appropriate for the finished product and a storage precaution relating to the protection of the product from light is not required.

Overall conclusion on quality

The applicant has provided data which are in line with current guidelines. Development pharmaceutics of the formulation is satisfactorily explained. The product is a simple aqueous solution which utilises standard pharmaceutical excipients. The manufacturing process is described in detail and is suitable to provide finished product of constant quality. Stability of both the active substance and finished product has been demonstrated.

3. Safety assessment and residues

A. Safety assessment

Pharmacodynamics

This application has been submitted under Article 3(3) of Regulation (EC) No 726/2004 in accordance with Article 13.1 of Directive 2001/82/EC, as amended and therefore pharmacodynamic data are not presented.

Pharmacokinetics

In accordance with Article 13.1 of Directive 2001/82/EC, as amended, *'The applicant shall not be required to provide the results of the safety and residue tests or of the pre-clinical and clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 5 for not less than eight years in a Member State of the Community.'*

As stated in Article 13 2(b), *'generic medicinal product shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.'*

Article 13 2(b) of the Directive goes on to state that *'Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines'*. In line with this provision, the applicant claimed an exemption from the requirement to provide the results of appropriate bioavailability studies on the basis that the test product:

- has the same pharmaceutical form (i.e. solution for injection) as the reference product
- is to be parenterally administered as a solution.
- contains the same active substance and excipients in the same concentrations as a veterinary medicinal product currently approved for use in the target species.

In relation to the third bullet, the applicant claimed that Recocam 20 mg/ml is identical in formulation to the reference product Metacam 20 mg/ml with the exception of one excipient (a chelating agent). In justifying the similarity in compositions between Recocam 20 mg/ml and the reference product Metacam 20 mg/ml, the applicant performed a quantitative analysis of the reference product.

Given that the applicant has provided definitive information on the quantitative composition of the reference product and that the only difference between the test and reference products is in respect of the chelating agent, it can be accepted that this difference is unlikely to have any effect on the bioavailability of meloxicam. The omission of bioequivalence studies can be accepted in accordance with paragraph 4(b) of the CVMP Guidelines for the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-Final).

User safety

Although no user safety assessment has been provided, it is considered that given the legal basis of the application (Article 13.1 – generic application) and the fact that the formulations of the test and reference products are claimed as being identical (with the exception of the chelating agent), there will not be any difference in user exposure scenarios and the same user warnings already accepted for the reference product Metacam 20 mg/ml are applicable to Recocam 20 mg/ml.

The following user warnings are included in section 4.5 of the SPC:

- Accidental self-injection may give rise to pain. People with known hypersensitivity to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should avoid contact with the veterinary medicinal product.
- In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

In conclusion, it is accepted that the omission of a specific user safety assessment for Recocam 20 mg/ml is justified and that the risk to the user will be identical to that posed by the reference product Metacam 20 mg/ml.

Environmental risk assessment

The applicant has provided a Phase I environmental risk assessment in line with current guidelines. The environmental risk assessment for Recocam 20 mg/ml solution for injection ends in Phase I, as the product will be used to treat individual animals or a small number of animals in a herd, and therefore it is concluded that the product will not pose an unacceptable risk to the environment.

B. Residue assessment

Depletion of residues

No data provided.

MRL

The active substance in Recocam 20 mg/ml solution for injection for cattle, pigs and horses is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No. 37/2010:

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

The excipients listed in section 6.1 of the SPC (with the exception of meglumine) are allowed substances for which table 1 of the annex to Commission Regulation (EU) No. 37/2010 indicates that no MRLs are required. The excipient meglumine is included in the list of substances considered as not falling within the scope of Council Regulation (EC) NO. 470/2009.

Withdrawal period

Given that the applicant has provided definitive information on the quantitative composition of the reference product and that the only difference between the test and reference products is in respect of the chelating agent, the CVMP accepted that this difference is unlikely to have any effect on uptake of meloxicam from the injection site or bioavailability.

The CVMP agreed that the following withdrawal periods authorised for the reference product Metacam 20 mg/ml solution for injection are applicable to Recocam 20 mg/ml solution for injection:

Cattle:	Meat and offal: 15 days	Milk: 5 days
Horses:	Meat and offal: 5 days.	
Pigs:	Meat and offal: 5 days.	

Overall conclusions on safety and residues

This application has been submitted under Article 3(3) of Regulation (EC) No 726/2004 in accordance with Article 13.1 of Directive 2001/82/EC. The applicant has claimed that Recocam 20 mg/ml is identical in formulation to the reference product Metacam 20 mg/ml with the exception of one excipient.

The applicant provided definitive information on the quantitative composition of the reference product with the only difference between the test and reference products being in respect of the chelating agent. Disodium edetate is included at a concentration of 0.2% in the reference product and citric acid is included at a concentration of 0.1% in Recocam. The CVMP accepted that the difference in chelating agents and the low concentration is unlikely to have any effect on uptake of meloxicam from the injection site or on bioavailability. Under these circumstances, the omission of bioequivalence studies was accepted in accordance with paragraph 4(b) of the CVMP Guideline for the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-Final).

Given the justification for the omission of bioequivalence studies, it can be accepted that no data in respect of pharmacology or toxicology are required. Further, based on the information presented, it is accepted that the risk to the user will be identical to that posed by the reference product Metacam 20 mg/ml and that the user safety statements proposed for inclusion in the SPC for Recocam 20 mg/ml are appropriate.

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

It can be accepted that the withdrawal periods for the reference product Metacam 20 mg/ml solution for injection can be applied to the test product Recocam 20 mg/ml solution for injection.

4. Efficacy assessment

Given that the applicant has provided definitive information on the quantitative composition of the reference product and that the only difference between the test and reference products is in respect of the chelating agent, it can be accepted that this difference is unlikely to have any effect on bioavailability, that bioequivalence can be assumed and that there will be no difference between products in respect of the efficacy profile.

Target animal tolerance

No data were provided. The applicant claimed that Recocam 20 mg/ml is identical in formulation to the reference product Metacam 20 mg/ml with the exception of one excipient (a chelating agent) and has consequently claimed an exemption from the demonstration of bioequivalence in line with paragraph 4(b) of the CVMP 'Guidelines for the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-Final)'.

It can be accepted that the replacement of disodium edetate with citric acid is unlikely to have a significant effect of the bioavailability of the active substance meloxicam following parenteral administration. Similarly, it can be accepted that the excipient citric acid, at the quantities included in the test formulation, is unlikely to have an adverse effect on local tolerance. It was noted that citric acid is a common excipient in veterinary medicinal products and is included in a number of products authorised for parenteral administration. The applicant's justification for the absence of tolerance studies was accepted.

5. Benefit risk assessment

Introduction

This application concerns the active substance meloxicam (a NSAID) and is submitted under Article 3(3) of Regulation (EC) No 726/2004 in accordance with Article 13.1 of Directive 2001/82/EC (a generic application). The proposed indications are identical to those included in the SPC of the reference product Metacam 20 mg/ml solution for injection for cattle, pigs and horses.

Benefit assessment

Direct therapeutic benefits

It is considered that direct therapeutic benefits result from the claimed efficacy of the product in reducing clinical signs associated with

- respiratory disease in cattle, diarrhoea in calves and young non-lactating cattle and acute mastitis in cattle
- non-infectious locomotor disorders in pigs and puerperal septicaemia and toxaemia in sows
- acute and chronic musculo-skeletal disorders in horses.

and consequently may be considered to benefit animal welfare and aid in the control of inflammatory symptoms associated the disorders specified in section 4.2 of the SPC.

Additional benefits

Indirect or additional benefits may be considered to arise from the reduction in severity of illness in the above conditions which will consequently have a positive benefit in respect of improved herd production levels and productivity.

Risk assessment

Given the nature of the active substance (NSAID) it is considered that the following animals will be at risk of increased toxicity following administration of the product:

- foals less than 6 weeks of age and in diarrhoeic calves less than 1 week old.
- Animals suffering from impaired hepatic, cardiac or renal function and haemorrhagic disorders.
- Animals showing evidence of ulcerogenic gastrointestinal lesions.
- Animals with hypersensitivity to the product or to any of the excipients.
- Dehydrated, hypovolaemic or hypotensive animals

Although use of the product in pregnant cows and sows is indicated, use of the product in pregnant mares is not.

Given the nature of the active substance (NSAID) it is considered that the following circumstances may result in an increased risk of toxicity following administration of the product:

- Simultaneous use with another NSAID or a glucocorticoid.
- Simultaneous use with an anticoagulant

The following user risks have been identified:

- Possible anaphylactoid-type reactions in people with hypersensitivity to the active substance meloxicam or any of the excipients.
- Accidental self-injection may give rise to pain

The following target animal tolerance risks have been identified:

- Transient local swelling at the injection site following subcutaneous administration of the product to cattle.
- Transient local swelling at the injection site following intravenous administration of the product to horses.

Risk management or mitigation measures

The applicant has included the same contra-indications, target animal safety warnings and user warnings in relevant sections of the SPC as those included in the SPC of the reference product Metacam 20 mg/ml solution for injection and this is considered appropriate.

Given that the formulation of the product Recocam 20 mg/ml is accepted as being essentially similar to that of the reference product Metacam 20 mg/ml, similar risk management and mitigation measures are applicable to Recocam 20 mg/ml as are approved for the reference product Metacam 20 mg/ml.

Evaluation of the benefit risk balance

It can be accepted that the product will have a similar benefit/risk profile to that of the reference product.

The product is expected to be well tolerated by the target animals and presents a low risk for users and the environment and appropriate warnings have been included in the SPC. A sufficient withdrawal period has been set.

Conclusion on benefit risk balance

Given the nature of the application (a generic) and the fact that the formulation of both the test and reference products can be considered to be similar, the CVMP considered that the benefits and the risks for both Recocam 20 mg/ml solution for injection and the reference product Metacam 20 mg/ml solution for injection should be the same.

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/EEC as amended.