22 August 2011
EMA/424555/2011
Veterinary Medicines and Product Data Management

Scientific discussion

This module reflects the initial scientific discussion for the approval of Emdocam (as published in August 2011). For information on changes after this date please refer to module 8.

1. Summary of the dossier

On 9 June 2011, the Committee for Medicinal Products for Veterinary Use (CVMP) adopted a positive opinion,[1] recommending the granting of a marketing authorisation for the veterinary medicinal product Emdocam, a meloxicam 20 mg/ml solution for injection intended for use in cattle, pigs and horses. The applicant for this veterinary medicinal product is Emdoka bvba.

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 (a generic application).

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

The benefits of Emdocam are the alleviation of inflammation and relief of pain in the approved indications. The most common side effects are a slight transient swelling at the injection site following subcutaneous administration in cattle, and in horses a transient swelling at the injection site.

The approved indication is:

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 musculoskeletal disorders. For the relief of pain associated with equine colic.

[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.

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2. Quality assessment

Composition

Emdocam is a generic medicinal product of a reference medicinal product previously authorised by the Community, Metacam 20 mg/ml solution for injection, for which the marketing authorisation holder (MAH) is Boehringer Ingelheim Vetmedica GmbH.

Emdocam, like the reference medicinal product Metacam, is an aqueous solution for injection and consists of the active substance meloxicam (20 mg/ml) and the excipients ethanol (preservative), poloxamer 188, meglumine, glycine, polyethylene glycol (macrogol) 300, sodium hydroxide, hydrochloric acid and water for injections.

Container

The product is to be packaged in 50 ml, 100 ml and 250 ml clear Type I glass vials closed with bromobutyl bungs and aluminium caps.

Development Pharmaceutics

Like the reference product, the generic product contains the active substance at a concentration of 20 mg/ml meloxicam. The excipient ethanol (anhydrous) is included in the formulation of the generic product as an antimicrobial preservative at a concentration of 150 mg/ml, which is in line qualitatively and quantitatively with the preservative in the reference product, for which the SPC is publicly available. Further information on the composition details of the reference product, Metacam 20 mg/ml solution for injection for cattle, pigs and horses, is drawn from publicly available information on its SPC. The applicant has developed a preparation which is identical to the reference product but which excludes disodium diaminoethane-tetraacetic acid (Na_2-EDTA).

This generic product application was the subject of a CVMP Scientific Advice procedure (EMEA/V/SA/053/09/1) in which this difference in composition between the generic and reference product was considered. The applicant has investigated the influence of the omission of disodium EDTA from the generic product formulation in line with recommendations in Scientific Advice received from the CVMP. Furthermore the function of each of the chosen excipients is explained and justified with particular emphasis on those with a solubility function.

The suitability of terminal sterilisation was investigated during development studies and the product was found not to be heat labile. Arising from these studies, terminal sterilisation is the method of choice for the product as it affords the best sterility assurance.

No overages are included in this medicinal product.

Method of manufacture

The manufacturing formulae for batch sizes of the proposed range of batch sizes are presented. The manufacturing process is a simple conventional process involving the sequential addition and mixing of the excipients and active substance in water for injections followed by terminal sterilisation in its final container.

Process validation is presented for three batches which were then filled into all the proposed vial sizes.

Control of starting materials

Active substance

An active substance master file (ASMF) is provided for meloxicam sourced from one manufacturer. The active substance was demonstrated to comply with the current European Pharmacopoeia (Ph. Eur.) monograph for meloxicam and the data provided in both the 'Open' and 'Restricted' parts of the ASMF are acceptable. The stability data provided support the claimed retest period.

A valid certificate of suitability issued by the European Department for the Quality of Medicines (EDQM) is provided for the second source of the active substance. Stability data provided support the claimed re-test period.

Excipients

Each of the excipients complies with the relevant Ph. Eur. monograph, except the hydrochloric acid (25%) which is not the subject of a Ph. Eur. monograph, but does comply with the Swiss national Pharmacopoeia Helvetica and is also considered to be adequately controlled by the specification given.

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

All ingredients used in the product are of synthetic or vegetable origin. A declaration is provided stating that all the raw materials and the method of manufacture for this product are in compliance with the Ph. Eur. General Chapter 5.2.8 "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products".

Control tests during production

The in-process controls described in the dossier are satisfactory.

Control tests of 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

Finished product stability data are presented for three batches packaged as proposed for marketing, in the three vial sizes, which were stored at 25 °C/60%RH and also under accelerated conditions 40 °C/75%RH. 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 for all three batches and vial sizes referred to above. The study was continued for 28 days. All physico-chemical test results were within specification, however the number of piercings (broachings) of the vial during this in-use stability study did not adequately

simulate use of the product in clinical practice, therefore a warning is included on the labels and other product literature that the stopper should not be broached more than 50 times.

Photostability

Photostability studies performed on two batches of the product filled into 100 ml and 250 ml vials showed that only minor changes were observed, with results for all specification parameters remaining well within specification. The clear glass vials are considered to be appropriate for the finished product, and no storage precaution regarding protection of the product from light is therefore required.

Freeze-thaw

A freeze thaw study has been conducted on samples from each of the three stability batches. The vials were subjected to two freeze-thaw cycles before testing. No significant changes were observed.

Overall conclusion on quality

In general, Part 2 of the dossier is of good quality and takes into account current rules and guidelines. Development pharmaceutics of the formulation is satisfactorily explained. The product is a simple aqueous solution for injection which utilises standard pharmaceutical excipients. The manufacturing process is described in detail and is suited to provide a finished product of constant quality. The active substance is the subject of a monograph in the Ph. Eur. The control tests of the finished product cover the relevant quality criteria and are suited to confirm adequate and constant product quality. Stability of both the active substance and the formulated product has been demonstrated. The shelf-life, in-use shelf-life and absence of specific storage precautions for the finished products have been justified.

3. Safety assessment and residues

A. Safety assessment

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 claimed an exemption from the requirement to provide the results of appropriate bioavailability studies in accordance with section 4(b) of the CVMP 'Guidelines for the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-Final)' 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 (that is, the reference product).

In relation to the third bullet point, the applicant claimed that Emdocam 20 mg/ml solution for injection is identical in formulation to the reference product Metacam 20 mg/ml solution for injection except for one excipient: the reference product Metacam 20 mg/ml contains 0.1% EDTA, which is not present in Emdocam 20 mg/ml. The applicant illustrated the similarity of Emdocam and the reference product (Metacam) by referring to the authorised SPC of the reference product and by analytical verification.

Based on the above, the omission of bioequivalence studies is justified in accordance with section 4(b) of the CVMP 'Guidelines for the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-Final)'. Indeed, the applicant sought scientific advice from the CVMP with respect to this specific point. Given the similarity in formulations, CVMP advised as follows: "*Provided the*

company convincingly shows that the solution is stable, without risk of precipitation also under stressed conditions, no in vivo studies (bioequivalence or residue studies) will be needed for any of the indicated species". The probable influence of the omission of EDTA on the quality of the formulation was investigated and it was accepted that the absence of EDTA is unlikely to have any significant effect.

Given that bioequivalence of the test and reference products was accepted, the Committee agreed that no data in respect of pharmacology or toxicology are required.

User safety

Although no user safety assessment was provided, the Committee 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 essentially the same (with the exception of EDTA), there will not be any difference in user exposure/risk and the same user warnings already accepted for the reference product Metacam 20 mg/ml are applicable to Emdocam.

In conclusion, the omission of a specific user safety assessment for Emdocam was accepted as is the conclusion that the risk to the user will be similar to that posed by the reference product Metacam 20 mg/ml.

The following user safety statements are proposed:

- Accidental self-injection may give rise to pain. People with known hypersensitivity to NSAID 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.

Appropriate user warnings are included in section 4.5 of the SPC.

Environmental safety

A Phase I environmental risk assessment was provided in line with current guidelines. It can be concluded that the environmental risk assessment for Emdocam 20 mg/ml solution for injection ends in Phase I and that the product will not pose an unacceptable risk to the environment, when used in accordance with the directions on the label. An appropriate sentence is included in section 6.6 of the SPC.

B. Residue assessment

Information has been provided by the applicant to illustrate the similarity in formulations between Emdocam 20 mg/ml solution for injection and the reference medicinal product, Metacam 20 mg/ml solution for injection, in respect of the excipients included in the formulations.

Depletion of residues

Based on the information provided, and noting the outcome of the CVMP Scientific Advice procedure (EMEA/V/SA/053/09/1), the Committee accepted that the absence of EDTA from Emdocam was unlikely to have any effect on the depletion of residues from the injection site. Under these circumstances, it was also agreed that the omission of residue studies was justified.

MRL

The active substance in Emdocam 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:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissues	Other provisions	Therapeutic classification
Meloxicam	Meloxicam	Bovine, 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 are either allowed substances for which Table 1 of 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 period

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

4. Efficacy assessment

See Part 3 of this report.

Given that the proposed bioequivalence of the test and reference products was accepted, the CVMP agreed that there should be no difference between the two products in respect of their efficacy profiles, and that no efficacy data were therefore required for Emdocam 20 mg/ml solution for injection.

5. Benefit risk assessment

Benefit assessment

The application for Emdocam 20 mg/ml solution for injection for cattle, pigs and horses is a generic application and is submitted in accordance with Article 13.1 of Directive 2001/82/EC. 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.

Direct 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 musculoskeletal disorders in horses

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

Indirect benefits

Indirect 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 productivity.

Risk assessment

Given the nature of the active substance (meloxicam, an NSAID) it is considered that the following animals could be at risk of 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 potential risks to users 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

Appropriate information and warnings are included in the SPC and product information to minimise risks for the animals, the user and for the environment.

Evaluation of the benefit risk balance

In the opinion of CVMP, the information provided has demonstrated that the overall benefit/risk balance for this product is positive.

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 Emdocam 20 mg/ml solution for injection and the reference product Metacam 20 mg/ml solution for injection should be the same.

In addition, the applicant has justified the omission of bioequivalence studies in accordance with section 4(b) of the CVMP bioequivalence guidelines.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the application for Emdocam is approvable.

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.