EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

## Committee for Medicinal Products for Veterinary Use

# CVMP assessment report for an extension to the community marketing authorisation for Emdocam (EMEA/V/C/002283/X/0012)

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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# Introduction

The applicant Emdoka BVBA submitted on 31 October 2019 an application for an extension to the marketing authorisation for Emdocam to the European Medicines Agency (The Agency) in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I thereof.

On 17 February 2021, the CVMP adopted an opinion and CVMP assessment report.

On 26 April 2021, the European Commission adopted a Commission Decision granting the marketing authorisation for Emdocam.

Emdocam is a generic veterinary medicinal product for which the reference product is Metacam.

Emdocam is currently available as a 20 mg/ml solution for injection and is authorised for cattle, pigs and horses. It contains meloxicam, a non-steroidal anti-inflammatory drug (NSAID), and was authorised for use in the Union on 18 August 2011.

This extension application is for a new strength of 5 mg/ml solution for injection for use in cattle, pigs and, two new target species, dogs and cats.

The applicant applied for the following indications:

**Dogs:**

Alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders. Reduction of post-operative pain and inflammation following orthopaedic and soft tissue surgery.

**Cats:**

Reduction of post-operative pain after ovariohysterectomy and minor soft tissue surgery.

**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 the relief of post-operative pain following dehorning in calves.

**Pigs:**

For use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation. For the relief of post-operative pain associated with minor soft tissue surgery such as castration.

Emdocam solution for injection contains 5 mg/ml meloxicam and is presented in packs containing 1 vial of 20 ml and 50 ml (cats and dogs) and 50 ml, 100 ml and 200 ml for cattle and pigs.

The applicant is registered as an SME pursuant to the definition set out in Commission Recommendation 2003/361/EC.

The rapporteur appointed is Jeremiah Gabriel Beechinor and the co-rapporteur is Cristina Muñoz Madero.

The dossier has been submitted in line with the requirements for submissions under Article 19 of Commission Regulation (EC) 1234/2008 and Annex I thereof (extensions).

## *Scientific advice*

Not applicable.

### *MUMS/limited market status*

Not applicable.

# Part 1 - Administrative particulars

### *Detailed description of the pharmacovigilance system*

The applicant has provided a detailed description of the pharmacovigilance system (version 9, dated January 2016). The applicant has also provided a DDPS declaration indicating the same version of the DDPS has already been assessed and approved during previously submitted centralised applications. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

### *Manufacturing authorisations and inspection status*

Batch release of the dosage form takes place within the EU at Produlab Pharma B.V., Raamsdonksveer, Netherlands. A GMP Certificate issued by the Competent Authority of Netherlands, Medicines Evaluation Board based on an inspection carried out on 17 May 2017 is available on Eudra GMP.

The active substance is manufactured outside the EEA. A satisfactory Qualified Person's declaration is provided by the Qualified Person at the EU batch release site.

### *Overall conclusions on administrative particulars*

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

# Part 2 - Quality

### *Composition*

The product consists of the active substance meloxicam (5 mg/ml) and the excipients ethanol (preservative), meglumine, glycofurol, poloxamer 188, glycine, sodium chloride, sodium hydroxide, hydrochloric acid and water for injection. Like the reference medicinal product, the pharmaceutical form is a solution for injection.

### *Containers*

The product is packaged in 20 ml, 50 ml, 100 ml and 250 ml Type I colourless glass vials closed with bromobutyl rubber stoppers and sealed with aluminium caps. Each vial is presented in a cardboard box. Presentations differ for groups of target species with vials sizes of 20 ml and 50 ml for cats/dogs and 50 ml, 100 ml and 250 ml for cattle and pigs.

The glass vials comply with Ph. Eur. 3.2.1. glass Containers for Pharmaceutical use and the stoppers are in compliance with Ph. Eur. monograph 3.2.9. Rubber closures of containers for aqueous preparations for parenteral use. The rubber bungs have been tested for fragmentation as per Ph. Eur. 3.2.9 and a statement is included on the SPC limiting the number of broachings to 50 in line with the number of piercings for which satisfactory fragmentation studies have been conducted.

## *Development pharmaceutics*

The objective of pharmaceutical development studies was to develop a product as similar as possible to the reference product. There are two presentations of the reference product Metacam 5 mg/ml solution for injection (MAH Boehringer Ingelheim Vetmedica GmbH) - one presentation for dogs/cats and another presentation for cattle and pigs.

The product contains the active substance meloxicam at a concentration of 5 mg/ml. The excipient ethanol (anhydrous), at a concentration of 150 mg/ml, is included in the formulation of the generic product as an antimicrobial preservative in line with, qualitatively and quantitatively, the preservative present in the reference product, the SPC for which is publicly available. Further information on the composition details of the reference product, Metacam 5 mg/ml solution for injection for cattle, pigs and horses, is drawn from publicly available information on the SPC and also from analysis with validated methods (meglumine, poloxamer 188 glycofurol and sodium chloride) on several batches of the reference product, results of which are presented in the dossier. The applicant also determined the pH and relative density of same batches of reference product using Ph. Eur. 2.2.3 and Ph. Eur. 2.2.5 methods. Based on the results of this analysis, the formulation detailed in the dossier was established for the generic product for cats and dogs and for cattle and pigs. It is noted that apart from the excipient hydrochloric acid, a pH adjuster, the excipients are also qualitatively the same as those contained within the reference product. Based upon the comparative physicochemical analysis, the Applicant has indicated that the pH of the candidate formulation (8.65) is almost identical to that of the four batches of the reference formulation tested (8.58). Use of pH adjusters during manufacture is accepted practise to ensure the pH of the solution is optimised. Consequently, the CVMP accepts that any differences between candidate and reference formulations in respect of the excipient hydrochloric acid is unlikely to have any influence on the rate and/or extent of absorption of the active substance. With respect to the quantitative composition of the excipients, the analysis of the excipients in four batches of the reference product provided by the applicant is considered adequate to demonstrate that the excipients are present in similar amounts to those in the reference products. Terminal sterilisation is the method of choice for the product as it affords the best sterility assurance with no negative impact on product quality.

## *Method of manufacture*

The manufacturing formulation for the pilot scale batch sizes is presented and the proposed batch size for future commercial batches is provided. The manufacturing process is a simple process involving sequential addition and mixing of the excipients and active in water for injections. The product is terminally sterilised in its final container using the standard Ph. Eur. cycle. A narrative description and flow chart of the manufacturing process are provided.

Satisfactory process validation is presented for three pilot batches. All proposed vial sizes are represented among the vials filled from each of these batches. In accordance with *EMA/CHMP/CVMP/QWP/BWP/70278/2012 Rev. 1* Process validation for finished products – information and data to be provided in regulatory submissions a process validation scheme is provided for subsequent execution at production scale.

## *Control of starting materials*

### *Active substance*

The supplier of the active substance has an ASMF in support of their material. The active substance complies with the Ph. Eur. monograph for the meloxicam with additional limits for residual solvents. The data provided in the ASMF (Open and Restricted sections) is acceptable. Stability data to support a retest period of 3 years is presented for the active substance.

### *Excipients*

Compliance with Ph. Eur. is claimed for all product excipients except glycofurol which is not monographed in Ph. Eur. Glycofurol is not a new excipient as it is used in other authorised veterinary medicinal products within the EU. The specification proposed for glycofurol consists of limits for appearance, colour, identification, relative density, pH, refractive index, water, peroxides, chlorides, sulphates, related substances, assay and composition and is considered acceptable.

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

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

None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev 3). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

## *Control tests on the finished product*

The specifications proposed at release and shelf-life include tests for aspect, visible particles, extractable volume, pH, relative density, identification and assay of ethanol, identification and assay of meloxicam, meloxicam related substances and sterility. The specifications are considered appropriate to control the quality of the finished product. Test methods for identification and quantitative determination of meloxicam and related substances and the determination of the preservative are described and are accompanied by validation data in accordance with the VICH guidelines. Validation data for the test for sterility is also included in the dossier. Satisfactory information regarding the reference standards used for assay has been presented.

Batch analysis results are provided for three pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the proposed product specification.

## *Stability*

Finished product stability data is presented for three pilot scale batches packaged as proposed for marketing in various vial sizes. The stability studies have been designed in accordance with VICH GL3

Stability testing of new veterinary drug substances and medicinal products:

- Vials stored at 25°C/60%RH will be tested after 3, 6, 9, 12, 18, 24 and 36 months.

- Vials stored at 40°C/75%RH will be tested after 3 and 6 months.
- Vials stored at 30°C/65%RH will only be tested if deemed necessary after evaluation of the results at 40°C/75%R.H. If necessary, vials will be tested after 6, 9 and 12 months at 30°C

Currently 24 months of data is available at 25°C/60%RH and at 30°C/65%RH and 6 months at 40°C/75%RH. Based on extrapolation of 24-month real time data, a shelf-life of 36 months is accepted, with no special storage precautions.

In-use stability

In-use stability was performed for all three pilot scale batches. The 20 ml, 100 ml and 250 ml vials were represented with 2 vials of each vial size tested at 9 months following manufacture. Based on the data presented an in-use shelf life of 28 days is accepted. Confirmation that in-use stability studies will be repeated on an aged batch close to the end of its shelf-life is provided.

No photostability studies or studies in inverted vials are presented. However, as this application is for a line extension (additional strength), the formulation of which is very similar to the original formulation, it is considered acceptable to extrapolate data from the original formulation. Stability studies for the original formulation showed comparable results for upright and inverted bottles. Photostability studies for the original formulation demonstrated that it is not light sensitive and additional storage precautions with respect to light sensitivity are therefore not considered necessary for this formulation.

### *Overall conclusions on quality*

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The active substance complies with the Ph. Eur. monograph for the meloxicam with additional limits for residual solvents and particle size. The data provided in the ASMF of the supplier (Open and Restricted sections) is acceptable. Stability data to support a retest period of 3 years is presented for the active substance.

Compliance with Ph. Eur. is confirmed for all product excipients except glycofurol which is not monographed in any pharmacopoeia. A satisfactory specification is provided for this excipient. The finished product specifications proposed at release are satisfactory and appropriate for control of the dosage form.

The real time stability studies for the dosage form is on-going. The data currently available supports the proposed shelf life of 3 years with no specific storage precautions and in-use shelf life of 28 days.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

## Part 3 – Safety

This application is for the introduction of a new 5 mg/ml strength formulation of Emdocam, which is currently authorised as a 20 mg/ml solution for injection for use in cattle and pigs. The application for this

generic product has been submitted in accordance with Article 19 of Commission Regulation (EC) 1234/2008 and Annex I thereof (extensions).

Emdocam 20 mg/ml solution for injection was authorised via the centralised procedure on 18 August 2011. The applicant cites three reference veterinary medicinal products: Metacam 1.5 mg/ml oral suspension for dogs, Metacam 5 mg/ml solution for injection for cattle and pigs and Metacam 5 mg/ml solution for injection for dogs and cats. All three reference products are considered part of the same global marketing authorisation, which has been authorised within the Community for not less than 10 years based on a full dossier and can be accepted as being suitable reference products.

## *Safety documentation*

## *Pharmacodynamics*

No data relating to the pharmacodynamic effects of the product have been provided.

Given that bioequivalence of this generic product with the reference product is considered to have been suitably supported (see pharmacokinetic section below) and that the generic product is intended to be administered to the same target species for the same indications at the same posology using the same routes of administrations as the reference product, the pharmacodynamics of meloxicam in the target species are not expected to differ between candidate and reference formulations. Consequently, the omission of pharmacodynamic data is justified.

The applicant proposes to include the same information in sections 5.1 of the proposed SPC as already approved for the centrally authorised reference product and this is considered acceptable.

## *Pharmacokinetics*

No data relating to the pharmacokinetic properties of the product have been provided.

The applicant claims essential similarity between the candidate product Emdocam 5 mg/ml and the reference product, Metacam 5 mg/ml solution for injection, based on chemical and physico-chemical equivalence.

The applicant proposes to waive the requirement for *in vivo* bioequivalence studies based on section 4.d of the CVMP 'Guideline for the conduct of bioequivalence studies for veterinary medicinal products' (EMEA/CVMP/016/00-corr-FINAL), claiming that the candidate formulation contains the same active substance and excipients in the same concentrations and has the same physico-chemical properties (pH, relative density) as the reference product. The applicant has also proposed a biowaiver in accordance with section 7.1.d of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) in part 2 of the dossier.

However, the claimed exemptions are inappropriate for the formulation in question and the applicant has referenced an outdated guideline from 2001. The applicable guideline is the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/2000-Rev.3-corr.), revised in December 2018. In accordance with this revised guidance, a bioequivalence waiver can be accepted based on section 7.1.a (relevant to the proposed intravenous use):

'The product is to be administered solely as an aqueous intravenous solution containing the same active substance as the currently approved product. However, if any excipients interact with the active substance (e.g. complex formation), or otherwise affect the disposition of the active substance, a bioequivalence study is required unless both products contain the same excipients in very similar quantity

and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance;'

and section 7.1.b (relevant to the proposed intramuscular and subcutaneous use):

'For products intended for intramuscular, subcutaneous or systemically acting topical administration, bioequivalence studies are not required in cases when the product is of the same type of solution, contains the same concentration of the active substance and comparable excipients in similar amounts as the reference veterinary medicinal product, if it can be adequately justified that the difference(s) in the excipient(s) and/or their concentration have no influence on the rate and/or extent of absorption of the active substance'.

Based on publicly available information (the SPC of the reference products Metacam 5 mg/ml solution for injection for cattle and pigs, and for dogs and cats), it can be accepted that the candidate formulation is qualitatively and quantitatively the same in terms of the active substance and the excipient ethanol. With the exception of the excipient hydrochloric acid, a pH adjuster, all excipients in the candidate product are also contained in the reference product.

Studies to compare the quantitative composition of the excipients and physicochemical properties of the candidate and reference formulations have been included in part 2 of the dossier. With respect to the quantitative composition of the excipients, the analysis of the excipients in four batches of the reference product provided by the applicant is considered adequate to demonstrate that the excipients present in the candidate product are similar in amounts to those in the reference product. Further, based on the comparative physicochemical analysis, the applicant has demonstrated that the pH of the candidate formulation (8.65) is almost identical to that of the four batches of the reference formulation tested (8.58). Consequently, it can be accepted that any differences between candidate and reference formulations in respect of the excipient included as a pH adjuster (hydrochloric acid) is unlikely to have any influence on the rate and/or extent of absorption of the active substance.

Based on the data/argumentation provided, it can be accepted that the candidate formulation is sufficiently similar to the reference formulation to be considered the same. Therefore, on the basis of sections 7.1.a and 7.1.b of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/00-Rev.3-corr.), bioequivalence can be accepted in the absence of *in vivo* study data and cross-reference to the safety and efficacy parts of the dossier of reference product is considered appropriate.

The applicant has proposed including the same information in section 5.2 of the proposed SPC as already approved for the centrally authorised reference product and this is considered acceptable.

## *Toxicological studies*

No data presented.

Given that bioequivalence of this generic product with the reference product is accepted, the omission of toxicological data is justified.

It is noted that the warnings included in section 4.3 and 4.7 of the proposed SPC are in line with those that appear on the SPC of the reference product. In accordance with the QRD template version 8.2, the SPC section 4.3 contains an additional warning related to a potential risk in animals with known hypersensitivity.

### *Single dose toxicity*

No data presented.

### *Repeat dose toxicity*

No data presented.

### *Tolerance in the target species of animal*

See part 4.

### *Reproductive toxicity*

No data presented.

### *Genotoxicity*

No data presented.

### *Carcinogenicity*

No data presented.

### *Studies of other effects*

No data presented.

### *Excipients*

No data presented.

### *User safety*

The applicant has not provided a user risk assessment.

Based on the information presented in part 2, it is accepted that the applicant has suitably demonstrated that the candidate formulation is sufficiently similar to the reference formulation to be considered the same. It can therefore be reasonably concluded that no difference in terms of risk to the user is to be expected between candidate and reference formulations and, consequently, the provision of user safety data is unnecessary in this instance. Furthermore, the product is intended to be administered to the same target species using the same routes of administration at the same dose rate as already approved for the reference product and the currently authorised product Emdocam 20 mg/ml. However, the proposed user safety warnings were not identical to those approved for the reference product. The sentence 'This product can cause eye irritation. In case of contact with the eyes, immediately rinse thoroughly with water' was therefore added in section 4.5ii of the SPC.

Based on the above risk assessment, the CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

## *Environmental risk assessment*

A phase I environmental risk assessment (ERA) was provided according to the relevant CVMP/VICH guidelines.

The environmental assessment can conclude at phase I, question 17, as the $PEC_{soil\ initial}$ value is below the phase II trigger value of 100 µg/kg. The omission of a phase II assessment can be accepted.

The standard disposal statement proposed by the applicant for inclusion in SPC section 6.6 is the same as that previously agreed by the CVMP for the reference products and can therefore be applied to the candidate product.

The CVMP concludes that the candidate formulation will not present an unacceptable risk for the environment when handled, used, stored and disposed of in accordance with the recommendations included in the proposed SPC.

## *Residues documentation*

The applicant has not provided residue depletion studies.

Based on the data/argumentation provided (similarity of formulations in terms of composition and physico-chemical properties), it can be accepted that the applicant has suitably demonstrated that the candidate formulation is sufficiently similar to the reference formulation to be considered the same. As a result, it is accepted that depletion of residues of meloxicam from the subcutaneous injection site in cattle and the intramuscular injection site in pigs is not expected to differ between candidate and reference formulations. On account of this and, given that the candidate formulation is to be administered to the same target species using the same route of administration and the same posology as already approved for the reference product, the absence of studies investigating depletion of residues from the injection site is justified.

The active substance is an allowed substance as described in Table 1 of the Annex to Commission Regulation (EU) 37/2010 as follows:

| Pharmacologically active substance | Marker residue | Animal species | MRL | Target tissues | Other provisions | Therapeutic classification |
|---|---|---|---|---|---|---|
| Meloxicam | Meloxicam | Bovine, caprine, porcine, rabbit, Equidae | 20 µg/kg<br>65 µg/kg<br>65 µg/kg | Muscle<br>Liver<br>Kidney | NO ENTRY | Anti-inflammatory agents/Nonsteroidal anti-inflammatory agents |
| | | Bovine, caprine | 15 µg/kg | Milk | | |

With the exception of glycofurol, the excipients listed in section 6.1 of the SPC are either allowed substances listed in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 or are included in the list of substances considered as not falling within the scope of Regulation (EC) No 470/2009 or are considered not to be pharmacologically active at the proposed concentrations and may therefore be considered safe for the consumer when the product is used in accordance with the recommendations in the proposed SPC.

Meglumine is included in the CVMP list of substances considered as not falling within the scope of Regulation (EC) 470/2009 at doses of up to 1.5 mg/kg bodyweight. Given that this excipient is included

in the candidate product at the rate of 3 mg/ml it can be accepted that when the test product is administered at the highest dose rate (0.5 mg/kg in cattle), the excipient meglumine will be administered below the limit of 1.5 mg/kg bodyweight and will not pose a risk in respect of consumer safety.

The applicant claims incorrectly that the excipient glycofurol is listed in Table 1 of the Annex to Commission Regulation (EU) No 37/2010. It is noted that this is not the case. However, the same excipient is included in the reference product and in the publicly available initial marketing authorisation document 'Metacam-EPAR-Scientific Discussion', the following is noted:

'For the excipient glycofurol, the Committee considered that at the concentration of the dose in the product to be administered to the target species, it would not be pharmacologically active and that an MRL would not be required'.

The CVMP accepts that the studies comparing the composition of the test item with that of the reference product that have been provided by the applicant indicate that this excipient is found at a similar concentration to that in the reference product and can therefore also be considered unlikely to be pharmacologically active. No concerns are raised in relation to the excipient glycofurol and it can be considered to fall outside the scope of Regulation (EC) No 470/2009 when used as in this product. The proposed withdrawal periods are identical to those approved for the reference product in the Community.

The CVMP accepts that the proposed withdrawal periods are adequate to ensure consumer safety.

## *Overall conclusions on the safety and residues documentation*

Based on the data provided in part 2, it is accepted that the criteria set out in sections 7.1.a and 7.1.b of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/2000-Rev.3-corr.) have been satisfied, that is, that the candidate formulation is of the same type of solution, contains the same concentration of active substances and comparable excipients in similar amounts as the reference product, and that any differences in their concentrations will have no influence on the rate and/or extent of absorption of the active substance. Consequently, bioequivalence between candidate and reference formulations can be assumed.

Further, as the test product is intended to be administered to the same target species using the same routes of administration at the same dose rate as already approved for the reference product, the omission of the results of safety tests can be accepted.

Pharmacology and toxicology

Due to the legal basis of this application and the fact that bioequivalence with the reference product is considered to have been suitably supported, no proprietary information has been submitted in support of the pharmacology and toxicology of the active substance. This can be accepted.

User safety

No user safety risk assessment has been provided. Based on the information presented in part 2, it is accepted that the applicant has suitably demonstrated that the candidate formulation is sufficiently similar to the reference formulation to be considered the same. It can therefore be reasonably concluded that no difference in terms of risk to the user is to be expected between candidate and reference formulations and, consequently, the provision of user safety data is unnecessary. Furthermore, the product is intended to be administered to the same target species, using the same routes of administration at the same dose rate as already approved for the reference product. However, the proposed user safety warnings are not identical to those approved for the reference product and therefore the sentence 'This product can cause eye irritation. In case of contact with the eyes, immediately rinse thoroughly with water' was added in section 4.5ii of the SPC.

It can be concluded that the candidate formulation will not present an unacceptable risk for the user when handled, used, stored and disposed of in accordance with the recommendations included in the proposed SPC.

Environmental safety

An environmental risk assessment has been provided by the applicant. It is concluded that the assessment can end at phase I as all $PEC_{soil\ initial}$ values fall below the trigger value of 100 µg/kg. It can be concluded that the candidate formulation will not present an unacceptable risk for the environment when handled, used, stored and disposed of in accordance with the recommendations included in the proposed SPC.

Consumer safety

No residue depletion studies were provided.

Based on the data/argumentation provided (similarity of formulations in terms of composition and physico-chemical properties), it is accepted that depletion of residues of meloxicam from the subcutaneous injection site in cattle and the intramuscular injection site in pigs is not expected to differ between candidate and reference formulations. The absence of studies investigating depletion of residues from the injection site is justified and extrapolation of the withdrawal periods approved for the reference product to the candidate product is appropriate.

It can be concluded that the candidate formulation will not present an unacceptable risk for the consumer when used of in accordance with the recommendations included in the proposed SPC.

# Part 4 – Efficacy

## *Bioequivalence*

This application has been submitted as an extension of the marketing authorisation for a generic veterinary medicinal product. The reference products cited are Metacam 5 mg/ml solution for injection for cattle and pigs and Metacam 5 mg/ml solution for injection for dogs and cats.

*In vivo* bioequivalence studies were not conducted. Instead, an exemption from such studies was accepted in accordance with sections 7.1.a and 7.1.b of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/00-Rev.3-corr.). Based on the data submitted, the CVMP considers that bioequivalence can be accepted in the absence of *in vivo* study data and cross-reference to the safety and efficacy parts of the dossier of the reference product is considered appropriate.

## *Pharmacodynamics*

See part 3.

## *Pharmacokinetics*

See part 3.

## *Dose justification/ Dose determination/ Dose confirmation studies*

No data on dose justification, dose determination or dose confirmation has been provided.

The product is an injectable solution containing meloxicam as the active substance, to be administered as a single injection to cattle intravenously or subcutaneously at a recommended dose rate of 0.5 mg meloxicam/kg bw, pigs intramuscularly at a recommended dose rate of 0.4 mg meloxicam/kg bw, dogs intravenously or subcutaneously at a recommended dose rate of 0.2 mg meloxicam/kg bw and cats subcutaneously at a recommended dose rate of 0.3 mg meloxicam/kg bw. The posology is justified by reference to the authorised SPC of the reference product.

As the bioequivalence between the candidate and reference products is considered to have been suitably supported, the omission of pre-clinical data is acceptable.

## *Target animal tolerance*

No data on target animal tolerance has been provided. As the bioequivalence between the candidate and reference products is considered to have been suitably supported, the omission of tolerance data is acceptable.

Commission Directive 2009/9/EC states:

*"For generic veterinary medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided:*

*— evidence to demonstrate target animal tolerance at the administration site, which may be substantiated by appropriate target animal tolerance studies."*

Based on the argumentation/data provided (similarity of formulations in terms of composition and physico-chemical properties), the CVMP accepts that tolerance at the administration site following intravenous or subcutaneous injection in cattle or dogs, intramuscular injection in pigs and subcutaneous injection in cats is not expected to differ between candidate and reference formulations.

Consequently, information included in sections 4.6 and 4.10 of the SPC approved for the reference product can be applied to the test product. It is noted that the warnings included in sections 4.3 and 4.7 of the proposed SPC are in line with those that appear on the SPC of the reference product. In accordance with the QRD template v.8.2, the SPC section 4.3 contains the additional warning relating to the potential risk in animals with known hypersensitivity.

## *Clinical studies*

No clinical study data has been provided.

Given the legal basis of this application, and the fact that bioequivalence with the reference product is considered to have been suitably supported, it can be accepted that the clinical efficacy profile of the candidate formulation will be the same as that of the reference formulation. As such, the omission of results of clinical trials can be accepted and the proposal to indicate use of the generic product for the same indications as already approved for the reference product using the same posology is considered acceptable.

### *Overall conclusion on efficacy*

This application has been submitted as an extension of the marketing authorisation for a generic veterinary medicinal product. The reference products cited are Metacam 5 mg/ml solution for injection for cattle and pigs and Metacam 5 mg/ml solution for injection for dogs and cats.

No pre-clinical or clinical study data has been provided. As the bioequivalence between the candidate and reference products can be accepted in accordance with sections 7.1.a and 7.1.b of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/00-Rev.3-corr.), the omission of such data is acceptable.

Given the legal basis of this application, and the fact that bioequivalence with the reference product is considered to have been suitably supported, it can be accepted that the efficacy profile of the candidate formulation will be the same as that of the reference formulation.

# Part 5 – Benefit-risk assessment

### *Introduction*

Emdocam is a solution for injection that contains 5 mg/ml of meloxicam as the active substance. The active substance is a well-known non-steroidal anti-inflammatory drug (NSAID) in veterinary medicine. The primary mode of action of meloxicam is inhibition of cyclooxygenases in the arachidonic acid inflammatory pathway. The product is intended for use in dogs, cats, cattle and pigs as an anti-inflammatory and/or antirheumatic.

The dossier has been submitted in line with the requirements for submissions in accordance with Article 19 of Commission Regulation (EC) 1234/2008 and Annex I thereof (extensions).

### *Benefit assessment*

## Direct therapeutic benefit

The evidence for the direct therapeutic benefit is considered established on the basis of bioequivalence to the reference product when administered at the same dose, route of administration and dosing interval as recommended in the marketing authorisation for the reference product.

## Additional benefits

No additional benefits for this generic veterinary medicinal product have been identified, other than the availability of an alternative product on the marketplace.

## Risk assessment

Given that bioequivalence with the reference product has been accepted, the risks associated with use of the product are expected to be the same as those of the reference product. Therefore, the product is not expected to present an unacceptable risk to the target animal, user or environment when used as recommended.

As possible risks to the user and the potential for adverse effects at the site of administration are identified in the SPC of the reference product, suitable risk mitigation measures and advice have been included in the proposed SPC (in line with what has been approved for the reference product) and this is considered adequate to mitigate the potential risks.

Meloxicam has been evaluated previously in respect to the safety of residues and MRLs have been established in Table I of the Annex to Regulation (EU) No 37/2010 for meat and offal from the target species concerned under this application. Emdocam 5 mg/ml is not expected to pose a risk to the consumer of meat and offal derived from treated animals when used according to the proposed SPC recommendations. The withdrawal periods established to ensure depletion of residues below the MRLs in meat and offal are the same as those of the reference product and are accepted, namely 15 days in cattle and 5 days in pigs.

*Quality:*

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

## *Risk management or mitigation measures*

Since bioequivalence between candidate and reference formulations has been accepted, it is considered appropriate that the warnings and risk mitigation measures proposed for inclusion in the SPC reflect those approved for the reference product. It is accepted that, for the risks identified in the SPC approved for the reference product, the same appropriate risk mitigation measures have been proposed for this generic product. However, the proposed user safety warnings are not identical to those approved for the reference product and the following sentence "*This product can cause eye irritation. In case of contact with the eyes, immediately rinse thoroughly with water*" was added in section 4.5ii.

## *Evaluation of the benefit-risk balance*

At the time of submission, the applicant applied for the following indication:

**Dogs:**

Alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders. Reduction of post-operative pain and inflammation following orthopaedic and soft tissue surgery.

**Cats:**

Reduction of post-operative pain after ovariohysterectomy and minor soft tissue surgery.

**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 the relief of post-operative pain following dehorning in calves.

**Pigs:**

For use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation. For the relief of post-operative pain associated with minor soft tissue surgery such as castration.

The product has been shown to be efficacious for these indications, and the CVMP accepted the indications as proposed by the applicant.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Based on the data presented, the overall benefit-risk is considered positive.

## *Conclusion*

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Emdocam 5 mg/ml is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above-mentioned medicinal product.