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/0013)

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 and 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 a new strength, new pharmaceutical form and route of administration for horses.

The applicant applied for the following indication:

Alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses.

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 in accordance with 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 (dated January 2016) which fulfils the requirements of Directive 2001/82/EC. 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. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacture and batch release of such veterinary dosage forms, has been provided.

The active substance is manufactured outside the EEA. A Qualified Person's declaration is provided by the Qualified Person at the EU batch release site. For the site of micronisation, a GMP certificate is available for the site on Eudra GMP. The certificate references micronisation as a manufacturing activity. The certificate is issued with reference to the human Directive, 2001/83/EC which can be accepted given the nature of the manufacturing activity.

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 (15 mg/ml) and the excipients sodium benzoate, silica, colloidal anhydrous, xanthan gum, sorbitol 70 %, glycerol, saccharin sodium, xylitol, sodium dihydrogen phosphate dihydrate, citric acid monohydrate, honey aroma and purified water. Like the reference medicinal product, the proposed pharmaceutical form of Emdocam is an oral suspension.

Containers

The product is presented in a cardboard box containing one high density polyethylene bottle of 125 ml or 336 ml with a HDPE screw cap. A 24 ml polypropylene measuring syringe is included in the cardboard box. Justification for the proposed bottle sizes is provided based on the posology of the product. The HDPE material used in the bottles and the polypropylene stoppers are certified as complying with a number of EU Directives and Regulations including Regulation (EU) No 10/2011. The polypropylene material used in the measuring syringe is confirmed as complying with requirement for food contact materials.

Demonstration of compliance with Ph. Eur. 2.9.27. Uniformity of mass of delivered doses from multidose containers has been demonstrated for delivered doses of 2 ml, 4 ml, 12 ml and 24 ml. This data satisfactorily demonstrates compliance with the monograph at the maximum and minimum dose volumes as well as at two intermediate points on the graduation scale on the syringe.

Development pharmaceutics

The product has been formulated to be similar to the reference product Metacam 15 mg/ml oral suspension for horses. The product contains meloxicam at a concentration of 15 mg/ml and is presented as an oral suspension. The product has also been formulated to contain the preservative sodium benzoate at a concentration of 1.5 mg/ml. This is the same preservative system used in the reference product.

With reference to patents for the reference product (WO 99/49845 and WO 2011/046853) the formulation for the generic product was developed and in order not to infringe the later patent, the suspending agent/thickener used in the reference product (hydroxyethylcellulose) was replaced with xanthan gum. Having based the proposed formulation on the patents and the information in the SPC for the reference product, the applicant conducted analysis of a number of batches of the reference product to derive its final formulation.

At the time of submission of this application, the Applicant had not conducted an in-vivo bioequivalence study and claimed an exemption from the requirement to demonstrate in-vivo bioequivalence in accordance with section 7.1.d of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3). Exemption (7.1.d) states that the following criteria must be met:

"the formulations are identical (identical active substances and excipients as well as physicochemical properties [e.g. identical concentration, dissolution profile, crystalline form, pharmaceutical form and particle size distribution with identical manufacturing process])".

It can be accepted that the candidate formulation is qualitatively and quantitatively the same as the reference formulation in respect of the active substance (meloxicam) and the excipient sodium benzoate given that their quantitative composition is publicly available from the SPC of the reference product. There is an identified difference in the formulations with respect to the excipients xanthan gum and hyrdoxyethylcellulose. The results of tests comparing the viscosity of the candidate and reference formulations are provided and the inclusion of xanthan gum at a concentration of 2 mg/ml results in a very similar viscosity to different batches of the reference product. The excipient honey aroma is not listed in any pharmacopeia and it is therefore not possible to conclude that the qualitative composition of this excipient is the same in the reference product and the proposed formulation. No information is provided with respect to the comparability of the honey aroma used in the reference and generic products.

With respect to the physico chemical characteristics of the product, particle size and polymorphism were both considered and batches of the generic product and the active substances used in it were tested and compared to the reference product. Based on this analysis it is concluded that the active substance is micronised and a particle size specification is set for the active substances. However, due to the presence of agglomerates leading to difficulties in performing this analysis in the formulated products, it is not possible to definitively conclude that the polymorphic form and particle size of the reference and generic products are identical. No information is provided in the dossier with respect to the dissolution profile of the reference and proposed formulations.

Whilst the manufacturing process is not a novel one, it does involve production of a suspension which necessitates a number of mixing steps in order to achieve a homogenous suspension. The patent WO 99/49845 provided by the applicant in support of the formulation development, makes specific reference to the use of strong shear forces to stabilise the suspensions. No information has been provided to demonstrate that the manufacturing process used for this proposed formulation is identical to that used for the reference product and that the same strong shear forces are applied during manufacture.

However, the omission of an *in vivo* bioequivalence study was not accepted and subsequently the applicant provided the results of such a study. This is further discussed in part 4.

Method of manufacture

Manufacture involves the sequential mixing of the excipients followed by addition of the active substance, pH adjustment and homogenisation of the suspension. A narrative description and flow chart of the

process are presented in the dossier. The level of detail of the data provided with respect to the manufacturing process is acceptable.

Process validation is presented for three pilot batches, one of which included minor differences in the order of addition on the components during the manufacturing process. All three validation batches were filled into both vial sizes. In addition, 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 and particle size. 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 confirmed for all product excipients except honey aroma which is not monographed in any pharmacopoeia. The specification proposed for honey aroma is considered acceptable and confirmation is provided that this excipient is safe for oral use and use in food.

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, net content, pH, relative density, viscosity, uniformity of mass of delivered dose (Ph. Eur. 2.9.27), identification and assay of sodium benzoate, identification and assay of meloxicam, meloxicam degradation products and microbiological quality. A test for resuspendability is included on the shelf life specification. The specifications proposed at release and at the end of shelf-life are appropriate to control the quality of the finished product.

The analytical methods used have been adequately described and, when necessary, appropriately validated in accordance with the VICH guidelines.

Test methods for identification and quantitative determination of meloxicam and degradation products and the determination of the preservative are described and are accompanied by validation data in accordance with the VICH guidelines. Satisfactory information regarding the reference standards used for assay has been presented.

Batch analysis results are provided for the 3 pilot scale batches used for process validation confirming the consistency of the manufacturing process and its ability to manufacture to the proposed product specification.

Stability

Stability tests were performed on three pilot scale batches of Emdocam 15 mg/ml oral suspension. Batches were manufactured at Produlab Pharma, Raamsdonksveer using two different batches of active substance sourced from the proposed active substance manufacturer. The finished product stability batches were filled into primary packaging of 125 and 336 ml.

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 tested after 3, 6, 9, 12, 18, 24, 30 and 36 months.
- Vials stored at 40°C/75%RH 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

The real time studies are completed to the end of the proposed shelf-life of 36 months, accelerated studies to 6 months with no issues identified necessitating testing at 30°C.

Based on the available stability data, the proposed shelf-life of 3 years with no specific storage precautions and in-use shelf life of 6 months as stated in the SPC are acceptable.

Overall conclusions on quality

At the time of submission of this application, the Applicant had not conducted an in-vivo bioequivalence study and claimed an exemption from the requirement to demonstrate in-vivo bioequivalence in accordance with section 7.1.d of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3). However, the omission of an *in vivo* bioequivalence study was not accepted and subsequently the applicant provided the results of such a study which demonstrated bioequivalence. This is further discussed in part 4.

Information on the, manufacture of the finished product has been presented in a generally satisfactory manner.

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 honey aroma which is not monographed in any pharmacopoeia. A satisfactory specification is provided for this excipient. The specifications proposed at release are satisfactory and appropriate for control of the dosage form.

The real time stability studies for the dosage form are completed to the end of the proposed shelf-life of 36 months and accelerated studies to 6 months. The data supports the proposed shelf life of 3 years with no specific storage precautions and in-use shelf life of 6 months.

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.

Part 3 – Safety

The application for the present generic product has been submitted in accordance with Article 19 of Commission Regulation (EC) 1234/2008 and Annex I thereof (extensions). The applicant cites the centrally authorised product Metacam 15 mg/ml oral suspension for horses (EU/2/97/004/009-030 — Boehringer Ingelheim Vetmedica GmbH) as the reference product. That product was granted a Community marketing authorisation on 7 January 1998 based upon a full dossier application. As the reference product has been authorised based upon a full dossier for in excess of 8 years, it can be accepted as a valid reference product for the purpose of this generic application.

Safety documentation

The product is an oral suspension that includes meloxicam as active substance at a concentration of 15 mg meloxicam per ml of product. The product is to be administered orally (either mixed with food or directly into the mouth) to horses for the alleviation of inflammation and relief of pain in both acute and chronic musculoskeletal disorders. The product is to be administered at a dose rate of 0.6 mg/kg bodyweight once daily for up to 14 days.

The concentration of active substance (meloxicam), the proposed target species, indication and posology are the same as those approved for the reference product.

The candidate formulation includes 15 mg/ml meloxicam as active substance and sodium benzoate, sorbitol, glycerol, saccharin sodium, xylitol, honey aroma, citric acid monohydrate, silica colloidal anhydrous, xanthan gum, sodium dihydrogen phosphate dihydrate and purified water as excipients.

It can be accepted that the candidate formulation is qualitatively and quantitatively the same as the reference formulation in respect of the active substance (meloxicam) and the excipient sodium benzoate, given that their quantitative composition is publicly available from the SPC of the reference product.

The applicant has presented the results of comparative analytical studies in part 2 of the application dossier and claims that the candidate formulation is qualitatively and quantitatively the same as the reference formulation in respect of the excipients sorbitol, glycerol, saccharin sodium, xylitol, sodium dihydrogen phosphate dihydrate, silica colloidal anhydrous, citric acid, honey aroma and purified water.

However, the applicant states that, in order to avoid infringing patent rights of the marketing authorisation holder of the reference product, the suspending agent/thickener hydroxyethylcellulose was replaced with xanthan gum in the candidate formulation.

Pharmacodynamics

No data on the pharmacodynamic properties of the product have been provided on the basis that the application is submitted as a generic application and that bioequivalence with the reference product (Metacam 15 mg/ml oral suspension for horses) is claimed.

The following information on the pharmacodynamic properties of meloxicam is proposed for inclusion in section 5.1 of the SPC and reflects the information included in the SPC approved for the reference product:

‘Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class which acts by inhibition of prostaglandin synthesis, thereby exerting anti-inflammatory, analgesic, anti-exudative and antipyretic effects. It reduces leucocyte infiltration into the inflamed tissue. To a minor extent, it also inhibits collagen-induced thrombocyte aggregation. Meloxicam also has anti-endotoxic properties because it has

been shown to inhibit production of thromboxane B_2 induced by intravenous *E. coli* endotoxin administration in calves and pigs'.

Given that this application has been submitted as a generic application and that bioequivalence with a reference product has been claimed, the omission of specific data on the pharmacodynamic properties of the product is appropriate, assuming that bioequivalence between candidate and reference products can be accepted.

The information proposed for inclusion in section 5.1 of the SPC is identical to that approved for the reference product and this is considered appropriate.

Pharmacokinetics

At the time of submission of this application, the applicant had not conducted *in vivo* comparative bioavailability studies and claimed that the omission of such studies can be accepted in accordance with the exemption set out in section 7.1.d of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/2000-Rev.3-corr.).

The applicant claimed that the candidate and reference formulations are qualitatively and quantitatively identical in respect to the active substance and all excipients, with the exception of the excipient hydroxyethylcellulose, which is present in the reference formulation but has been replaced with xanthan gum in the candidate formulation. The applicant's claim of identicality of quantitative composition between candidate and reference formulations for the other ingredients is based upon results of comparative analysis of the composition of the candidate and reference formulations and the results of comparative physico-chemical tests.

However, the omission of an *in vivo* bioequivalence study was not accepted and subsequently the applicant provided the results of such a study which demonstrated bioequivalence with the reference product.

The applicant proposes to include the same information in section 5.2 of the SPC as already approved for the reference product. Given that bioequivalence with the reference product has been demonstrated, this is considered acceptable. The information is as follows:

Absorption

When the product is used according to the recommended dosing regimen, the oral bioavailability is approximately 98%. Maximal plasma concentrations are obtained after approximately 2–3 hours. The accumulation factor 1.08 suggests that meloxicam does not accumulate when administered daily.

Distribution

Approximately 98% of meloxicam is bound to plasma protein. The volume of distribution is 0.12 L/kg.

Metabolism

The metabolism is qualitatively similar in rats, mini-pigs, pigs, cattle and humans although quantitatively there are differences. The major metabolites found in all species were the 5-hydroxy- and 5-carboxy-metabolites as well as the oxalyl-metabolite. The metabolism in horses was not investigated. All major metabolites have been shown to be pharmacologically inactive'.

Bioequivalence

See part 4.

Toxicological studies

No toxicological data was provided on the grounds that the application has been submitted as a generic application and the applicant concludes that the results of single dose and repeat dose toxicity studies are not required.

Article 13.1 of Directive 2001/82/EC for generic products states that '[...] 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 […]'.

The applicant provided the results of an *in vivo* bioequivalence study. Based on the findings of this study, it can be accepted that the candidate product is bioequivalent to the reference product and, consequently, the omission of the results of safety tests (including single and repeat dose toxicity data) can be accepted.

Single dose toxicity

No data presented.

Repeat dose toxicity

No data presented.

Tolerance in the target species of animal

The tolerance in the target animal has been assessed under part 4.

Reproductive toxicity

Study of the effect on reproduction

No data presented.

Study of developmental toxicity

No data presented.

Genotoxicity

No data presented.

Carcinogenicity

No data presented.

It can be accepted that the candidate product is bioequivalent to the reference product and, consequently, the omission of carcinogenicity data can be accepted.

Excipients

It can be accepted that all of the excipients used in the candidate formulation are commonly used in veterinary medicinal products and all (apart from xanthan gum) are included in the reference product formulation. Consequently, no specific risk in terms of safety of the excipients to the user, target animal, consumer or the environment has been identified.

User safety

No specific user safety assessment has been provided.

The applicant claims that, as the candidate formulation is identical to the reference formulation and is to be used in the same target species for the same indications at the same posology, the user safety warnings approved for the reference product may be applied to the candidate product.

The applicant's safety expert report states that the CVMP 'Guideline on user safety for pharmaceutical veterinary medicinal products' (EMEA/CVMP/543/03) does not apply to applications for marketing authorisations submitted in accordance with Article 13.1 of Directive 2001/82/EC.

Consequently, the following user safety warnings are proposed for inclusion in section 4.5 of the SPC which are the same as those approved for the reference product:

'People with known hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) should avoid contact with the veterinary medicinal product.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician'.

Article 13.1 of Directive 2001/82/EC states that '[...] 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 [...]'.

The applicant reviewed safety data for the excipient xanthan gum and, based on the data provided, it can be accepted that the inclusion of xanthan gum in the candidate formulation will not present an unacceptable risk to the user.

The applicant provided information clarifying that the closure of the immediate packaging is certified in accordance with ISO 8317 and the SPC has been updated to indicate that the screw cap is tamper-proof and child-resistant. This can be accepted.

Whilst it is noted that that the candidate product is intended to be presented in a maximum volume of 336 ml, which is greater than that authorised for the reference product (250 ml), it can be accepted that this in itself is unlikely to present an unacceptable risk to the user as the same dose will be withdrawn irrespective of product.

As bioequivalence with the reference product was demonstrated, the applicant proposes to include the same warnings in sections 4.5 and 4.7 of the proposed SPC as already agreed by the CVMP for the reference product. This is considered appropriate. 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.

Given the essential similarity between candidate and reference formulations, it can be accepted that the candidate formulation will not present any greater risk to the user than the reference formulation when

stored, handled, used and disposed of in accordance with the recommendations included in the proposed SPC.

Environmental risk assessment

An environmental risk assessment has been provided.

The safety expert indicates that a phase I environmental risk assessment has been conducted that takes into account the relevant categories of the target species cattle, pigs and horses.

However, as the proposed target species is horses, the applicant's safety expert reference to other target species (cattle and pigs) is irrelevant.

The applicant is of the opinion that harmful effects for the environment are not expected and concludes that, as the product will only be administered to individual animals, no $PEC_{soil\ initial}$ calculations are necessary and that the environmental risk assessment may stop in phase I.

The wording proposed for inclusion in section 6.6 of the SPC is the same as that approved for the reference product and as recommended in the most recent version (8.2) of the QRD template, namely:

'Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements'.

The applicant has provided a brief environmental risk assessment. In that assessment, the applicant highlights the fact that the proposed target species (horses) is considered a minor target species and, given the nature of the active substance (an NSAID), the product will only be used in individual animals.

According to question number 5 of the phase I decision tree (i.e. 'will the VMP be used to treat a small number of animals in a flock or herd?'), the phase I assessment may end at this question in the case of injectable NSAIDs on the basis that such products are expected to be used for the treatment of a 'small number of animals'.

Whilst the guideline specifically mentions injectable NSAIDs, it is understood that the possibility to end the ERA at this question is based on the assumption that the product in question will only be used for the treatment of a small number of animals.

Given the proposed target species (horses) and the fact that an ERA already exists for the active substance when administered to a major species, it can be accepted that the ERA may end at question number 5 of the phase I decision tree, as the product will only be used for the treatment of individual (or a small number) animals in the same way as an injectable NSAID.

Conclusions on the environmental risk assessment

An ERA was provided according to the relevant CVMP/VICH guidelines. Based on the data provided, the ERA can stop at phase I, as none of the phase I criteria are met.

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

Residues documentation

The product is an oral suspension that includes meloxicam as active substance at a concentration of 15 mg meloxicam per ml of product. The product is to be administered orally (either mixed with food or

directly into the mouth) to horses for the alleviation of inflammation and relief of pain in both acute and chronic musculoskeletal disorders. The product is to be administered at a dose rate of 0.6 mg/kg bodyweight once daily for up to 14 days.

The concentration of active substance (meloxicam), the proposed target species, indication and posology are the same as those approved for the reference product.

MRLs

The active substance meloxicam is included 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 65 µg/kg 65 µg/kg	Muscle Liver Kidney	NO ENTRY	Anti-inflammatory agents/Nonsteroidal anti-inflammatory agents
		Bovine, caprine	15 µg/kg	Milk		

Concerning the excipients sodium benzoate (E 211), sorbitol (liquid) (E 420), glycerol (E 422), saccharin sodium (E 954), xylitol (E 967), sodium dihydrogen phosphate dihydrate (E 339), silica colloidal anhydrous (E 551), xanthan gum (E 415) and citric acid monohydrate (E 330), it can be accepted that all are covered by the entry in Table 1 of the Annex to Commission Regulation (EU) 37/2010 for food additives ('substances with a valid E-number approved as additives in foodstuffs for human consumption') and for which no MRL is required. Further, all (with the exception of xanthan gum) are included in the formulation of the reference product.

Concerning the remaining two excipients (honey aroma and purified water), it can be accepted that both are also included in the reference formulation and have therefore previously been considered by the CVMP as not being pharmacologically active. Similarly, these substances are not considered to be pharmacologically active when used as in this product and therefore are not considered to fall within the scope of Regulation 470/2009.

Residue studies and withdrawal periods

The applicant claims that, in accordance with Article 13 of Directive 2001/82/EC, no product-specific residue depletion studies are required, as the candidate formulation is claimed to be identical to the reference product formulation, with the exception of the excipient hydroxyethylcellulose in the reference formulation which is replaced by xanthan gum in the candidate formulation.

The applicant concludes that the withdrawal period for meat and offal approved for the reference product (3 days) can be applied to the candidate product.

Article 13(1) of Directive 2001/82/EC states that '[...] 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 [...]'.

However, Title III.1 of Annex I to Directive 2001/82/EC indicates that, for generic veterinary medicinal products intended to be administered by the intramuscular, subcutaneous or transdermal routes,

evidence to demonstrate equivalent or differing depletion of residues from the administration site should be provided.

Given the proposed route of administration (oral), it can be accepted that the withdrawal period approved for the reference product may be applied to the candidate product.

The following information is proposed for inclusion in section 4.11 of the SPC:

'Meat and offal: 3 days'.

It is noted that section 4.3 of the proposed SPC includes the following advice:

'Do not use in pregnant or lactating mares'.

The above information/advice is identical to that approved for the reference product.

It is noted that no withdrawal period for milk has been proposed in line with the SPC of the reference product. The applicant proposes to contraindicate use of the product in mares producing milk for human consumption. However, it is considered appropriate that all information relating to consumer safety should be included in section 4.11 of the SPC.

Consequently, the following information was included:

'Do not use in mares producing milk for human consumption'.

Overall conclusions on the safety and residues documentation

This application has been submitted for a generic veterinary medicinal product. The applicant cites the centrally authorised product Metacam 15 mg/ml oral suspension for horses (EU/2/97/004/009-030 — Boehringer Ingelheim Vetmedica GmbH) as reference product.

The product is an oral suspension that includes meloxicam as active substance at a concentration of 15 mg meloxicam per ml of product. The product is to be administered to horses (either mixed with food or directly into the mouth) for the alleviation of inflammation and relief of pain in both acute and chronic musculoskeletal disorders at a dose rate of 0.6 mg/kg bodyweight once daily for up to 14 days.

Article 13.1 of Directive 2001/82/EC states that '[...] 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 [...]'.

The applicant provided the results of an *in vivo* bioequivalence study. Based on the findings of this study, it can be accepted that the candidate product is bioequivalent to the reference product and therefore toxicity data is not required.

No user safety assessment has been provided. However, the applicant justified that the inclusion of xanthan gum in the candidate formulation will not present an unacceptable risk to the user. This can be accepted.

The applicant provided information clarifying that the closure of the immediate packaging is certified in accordance with ISO 8317 and the SPC has been updated to indicate that the screw cap is tamper-proof and child-resistant. This can be accepted.

Given the essential similarity between the candidate and the reference formulation, it can be accepted that the candidate formulation will not present any greater risk to the user when stored, handled, used and disposed of in accordance with the recommendations included in the proposed SPC. However, the proposed user safety warnings are not identical to those approved for the reference product and 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.

A brief environmental risk assessment has been provided. According to question number 5 of the phase I decision tree (i.e. 'will the VMP be used to treat a small number of animals in a flock or herd?'), phase I assessment may end at this question in the case of injectable NSAIDs on the basis that such products are expected to be used for the treatment of a 'small number of animals'. Whilst the guideline specifically mentions injectable NSAIDs, it is understood that the possibility to end the ERA at this question is based on the assumption that the product in question will only be used for the treatment of a small number of animals.

As the proposed indications are identical to those already approved for the applicant's product 'Emdocam 20 mg/ml solution for injection for cattle, pigs and horses' (and for which an ERA already exists for the active substance when administered to a major species), it can be accepted that the product will only be used for the treatment of individual (or a small number) animals in the same way as an injectable NSAID.

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

It can be accepted that the active substance and all excipients in the candidate formulation are either included in Table 1 of Commission Regulation (EU) No 37/2010 or are not pharmacologically active when used as in this product and are therefore considered as falling outside the scope of Regulation 470/2009.

Based on the findings from the *in-vivo* bioequivalence study data, extrapolation of the same withdrawal period approved for the reference product to the candidate product is considered appropriate.

Part 4 – Efficacy

Bioequivalence

This application has been submitted as an extension of the marketing authorisation for a generic veterinary medicinal product. The reference product cited is Metacam 15 mg/ml oral suspension for horses. According to the definition of a generic medicinal product provided in Article 13.1 of Directive 2001/82/EC, bioequivalence with a reference product must be demonstrated by appropriate bioavailability studies.

The applicant provided the results of an *in vivo* bioequivalence study. Based on the findings of this study, it can be accepted that the candidate product is bioequivalent to the reference product.

Pharmacodynamics

No data on the pharmacodynamic properties of the product has been provided on the basis that Emdocam 15 mg/ml oral suspension for horses is a generic product and bioequivalence with the reference product (Metacam 15 mg/ml oral suspension for horses) is claimed.

Given that bioequivalence with the reference product has been demonstrated, the omission of specific data on the pharmacodynamic properties of the product is appropriate.

The information proposed for inclusion in section 5.1 of the SPC is identical to that approved for the reference product and this is considered appropriate.

Pharmacokinetics

The applicant provided the results of a GLP-compliant *in vivo* bioequivalence study comparing the candidate product with the reference product when administered to horses at a dose rate of 0.6 mg/kg meloxicam per kg body weight (corresponding to 0.4 ml of suspension per 10 kg body weight) on a single occasion and with a wash-out period of 7 days between treatments. 32 clinically healthy horses aged between 2 and 13 years and weighing between 437 and 670 kg were included in the study. The results of the ANOVA indicate that the 90% confidence intervals for the ratio of geometric means of test/reference product for the parameters C_{max} and AUC_t fall within the pre-specified acceptance limits of 70-143% and 80-125%, respectively and therefore based on the findings of this study, it can be accepted that the candidate product is bioequivalent to the reference product.

It can be accepted that the assay method used to determine meloxicam concentrations in equine plasma has been suitably validated.

Given that bioequivalence with the reference product has been demonstrated, the omission of specific data on the pharmacokinetic properties of the product is appropriate.

The applicant proposes to include the same information in section 5.2 of the SPC as already approved for the reference product and this is considered appropriate.

Dose justification/ Dose determination / Dose confirmation studies

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

On the grounds that Emdocam 15 mg/ml oral suspension for horses is a generic product, the applicant concludes that dose determination and dose confirmation studies are not required and such data may be extrapolated from the dossier of the reference product.

Given that bioequivalence between candidate and reference formulations has been demonstrated, the omission of pre-clinical data can be accepted and extrapolation of such data from the dossier of the reference product to the candidate product is appropriate.

Target animal tolerance

No data on target animal tolerance has been provided.

On the grounds that Emdocam 15 mg/ml oral suspension for horses is a generic product, the applicant concludes that target animal tolerance data is not required and data supporting tolerance in the target species may be extrapolated from the dossier of the reference product.

Given that bioequivalence between candidate and reference formulations has been demonstrated and the proposed route of administration (oral), the omission of target animal tolerance data can be accepted as no difference in tolerance between candidate and reference products is expected.

Clinical field trials / Clinical studies

No data relating to clinical field trials has been provided.

On the grounds that Emdocam 15 mg/ml oral suspension for horses is a generic product, the applicant concludes that clinical field trial data is not required and such data may be extrapolated from the dossier of the reference product.

Given that bioequivalence between candidate and reference formulations has been demonstrated, the omission of clinical data can be accepted. The clinical efficacy profile of the candidate formulation is expected to be the same as that of the reference formulation.

Overall conclusion on efficacy

This application has been submitted as an extension of the marketing authorisation for a generic veterinary medicinal product. The applicant cites the centrally authorised product Metacam 15 mg/ml oral suspension for horses (EU/2/97/004/009-030 - Boehringer Ingelheim Vetmedica GmbH) as reference product.

The product is an oral suspension that includes meloxicam as active substance at a concentration of 15 mg meloxicam per ml of product. The product is to be administered to horses (either mixed with food or directly into the mouth) for the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders at a dose rate of 0.6 mg/kg bodyweight once daily for up to 14 days.

The applicant provided the results of an *in vivo* bioequivalence study. Based on the findings of this study, it can be accepted that the candidate product is bioequivalent to the reference product.

No pre-clinical or clinical study data has been provided. As bioequivalence between the candidate and reference products has been demonstrated, 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 demonstrated, 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 an oral suspension that contains 15 mg/ml 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 horses for the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders.

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 proposed benefit of the product is its efficacy in alleviating inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses. As this is a generic application, the proposed

indication is the same as that already approved for the reference product and no efficacy data has been provided.

The evidence for the direct therapeutic benefit is claimed 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. Results of a GLP-compliant *in vivo* bioequivalence study have been provided and which demonstrate that the candidate product is bioequivalent to the reference product. Consequently, the direct therapeutic benefits are expected to be the same for the candidate and reference products.

Additional benefits

As this is a generic application and no additional data has been provided, no additional benefits are foreseen, other than the availability of an alternative product on the marketplace.

Risk assessment

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.

Safety:

As this is a generic application and bioequivalence with the reference product has been demonstrated, the safety aspects of the reference product can be extrapolated to the candidate product.

Risks for the target animal:

As this is a generic application and bioequivalence with the reference product has been demonstrated, no difference in tolerance between candidate and reference products is expected.

Risk for the user:

Given that the principle difference between candidate and reference formulations is the inclusion of xanthan gum in the candidate formulation, acceptable information on the safety of xantham gum for the user was provided. The closure of the immediate packaging is certified in accordance with ISO 8317 and can therefore be considered tamper-proof and child-resistant.

Given the essential similarity between candidate and reference formulations, it can be accepted that the candidate formulation will not present any greater risk to the user when stored, handled, used and disposed of in accordance with the recommendations included in the proposed SPC.

Risk for the environment:

The product is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk for the consumer:

It can be accepted that the active substance and all excipients in the candidate formulation are either included in Table 1 of Commission Regulation (EU) No 37/2010 or are not pharmacologically active and are therefore considered as falling outside the scope of Regulation 470/2009.

Based on the findings from the *in-vivo* bioequivalence study, extrapolation of the same withdrawal period approved for the reference product to the candidate product is considered appropriate.

Risk management or mitigation measures

As this is a generic application and bioequivalence with the reference product has been demonstrated, the risk mitigations measures and advice proposed for inclusion in the SPC are the same as those already agreed for the reference product.

User safety:

The same user safety warnings as already approved for the reference product have been included in the product information.

Environmental safety:

Standard advice on safe disposal of the product is proposed for inclusion in the product information and this is considered acceptable.

Consumer safety:

Given the absence of a proposed withdrawal period for milk, the following risk mitigation advice has been included in section 4.11 of the proposed SPC:

'Not authorised for use in horses producing milk for human consumption'.

Evaluation of the benefit-risk balance

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

Alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses.

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 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.