EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Metacam 40 mg/ml solution for injection for cattle and horses (EMEA/V/C/000033/X/0107)

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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Product profile

Invented name:	Metacam
Active substances:	Meloxicam
Target species:	Cattle and horses
Pharmaceutical form:	Solution for injection
Strength:	40 mg/ml
Therapeutic indication:	Cattle: For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle. For use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle. For adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy. For the relief of post-operative pain following dehorning in calves. Horses: For use in the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders. For the relief of pain associated with equine colic.
ATCvet code	QM01AC06
Pharmaco-therapeutic group	Anti-inflammatory and antirheumatic products, non-steroids (oxicams)
Applicant	Boehringer Ingelheim Vetmedica GmbH

Introduction

On 15 January 2014 Boehringer Ingelheim Vetmedica GmbH submitted an application for an extension to the Community marketing authorisation for Metacam to the European Medicines Agency (the Agency) in accordance with Article 19 of Commission Regulation (EC) No. 1234/2008 and Annex I point 2(c) thereof.

Metacam contains meloxicam, a non-steroidal anti-inflammatory substance, and was authorised for use in the Community on 7 January 1998 and has been the subject of a variety of variations and extensions.

This extension application is to add a new strength 40 mg/ml solution for injection for the existing target species cattle and horses. The route of administration is intravenous use. The rapporteur appointed was F. Hasslung-Wikström and co-rapporteur C. Ibrahim.

Metacam is authorised for the following indications in cattle and horses:

Cattle: For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs; for use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle; for adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy and for the relief of post-operative pain following dehorning in calves.

Horses: For use in the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders and for the relief of pain associated with equine colic.

The approved withdrawal period is 15 days for meat and offal and 5 days for milk in cattle and 5 days for meat and offal in horses. The product is not authorised for use in horses producing milk for human consumption.

Metacam 40 mg/ml solution for injection will be available in type I glass vials of 50 or 100 ml closed with a rubber stopper and sealed with an aluminium cap packed in cardboard boxes containing 1 or 12 vials.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

On 12 February 2015, the CVMP adopted an opinion and CVMP assessment report.

On 9 April 2015, the European Commission adopted a Commission Decision for granting an extension to the marketing authorisation for Metacam.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (dated November 2012, version 1.07) 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 European Union (EC) or in a third country.

Manufacturing authorisations and inspection status

The manufacturer of the finished product is appropriately authorised for manufacture of the product in accordance with European Union (EU) good manufacturing practice (GMP). A GMP certificate was provided. Batch release for the EU will be carried out by Produlab Pharma B.V., The Netherlands.

A statement from the qualified person (QP) of the manufacturer of the finished product confirming that the manufacture of the active substance is performed in compliance with GMP was provided.

The detailed description of the pharmacovigilance system and GMP certification of the manufacturing site of the finished product and the site responsible for batch release were considered in line with legal requirements.

In addition, the applicant was recommended to provide the following information post-authorisation:

Following the re-audit of the active substance manufacturing site, the applicant should provide an updated QP declaration as soon as it is available.

Part 2 - Quality

Composition

The new presentation is an aqueous solution for intravenous injection containing meloxicam at a concentration of 40 mg/ml.

The excipients used in the formulation (poloxamer 188, macrogol 300, glycine, disodium edetate, sodium hydroxide, hydrochloric acid and meglumine) are the same as those used for the solution for injection already authorised in other strengths. They are all well-known and widely used in other medicinal products, including other solutions for injection. The proposed composition includes 150 mg/ml of ethanol as antimicrobial preservative and several solubilising agents are included as the active substance is practically insoluble in water.

Metacam 40 mg/ml solution for injection is qualitatively identical to the 20 mg/ml solution and differs quantitatively only in the concentrations of the active substance (40 mg/ml vs. 20 mg/ml) and some excipients. The proportion between the active substance meloxicam and excipients has been appropriately justified by the applicant.

Container

The product is presented in colourless type I glass vials of 50 ml and 100 ml, closed with bromobutyl stoppers and aluminium caps. These are characteristic components for the primary packaging of solutions for injection.

Development pharmaceutics

The development pharmaceutics is acceptable. The rationale for the proposed composition is discussed and is acceptable. The formulation development performed is acceptable. All excipients used are already used in the approved 20 mg/ml strength. The proportion between the active substance meloxicam and excipients has been justified.

The sterilisation method used is acceptable.

The container closure system for the finished product is characteristic for this pharmaceutical form. Materials in contact with the solutions fulfil the specifications of the relevant European Pharmacopoeia (Ph. Eur.) monographs for the type I glass and for the bromobutyl stoppers. Fragmentation and self-sealing test have been conducted on the stoppers.

Method of manufacture

The manufacturing process is a standard one.

The justification that the proposed manufacturing process can be considered standard is in line with current guideline on process validation for finished products (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1). No validation data is included in the dossier, only the validation protocol has been provided. This is acceptable for a standard process.

Control of starting materials

Active substance

The active substance meloxicam is the subject of a Ph. Eur. monograph. The manufacturer of meloxicam has been granted a certificate of suitability of the Ph. Eur. (CEP) by the European Directorate for the Quality of Medicines and Healthcare (EDQM). The CEP is valid and a copy has been provided. Ph. Eur. chemical reference standards (CRS) for meloxicam and impurities are available. Meloxicam is controlled according to the tests of the Ph. Eur. monograph and the additional test included in the annex of the CEP. Data for one batch of active substance tested by the manufacturer of the finished product was provided. The batch data include all tests of the Ph. Eur. monograph and the additional test included in the CEP. Particle size and polymorphic form are also controlled.

Stability data were provided for 8 batches tested at 25 °C ± 2 °C /60% ± 5% relative humidity (RH) up to 60 months and at 40 °C ± 2 °C/75% ± 5% RH for 6 months. All results comply with the specification. The proposed retest period of 5 years is acceptable and considered justified by the stability data provided.

Excipients

The excipients used in the manufacture of the solution for injection are: ethanol, poloxamer 188, glycine, meglumine, macrogol 300, disodium edetate, water for injections, hydrochloric acid and sodium hydroxide. All excipients are the subject of a monograph in the Ph. Eur.

Certificates of analysis of the excipients from the manufacturer of the finished product have been submitted and are satisfactory.

The data provided for the excipients are considered acceptable.

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

None of the starting materials used for the manufacture of the active substance meloxicam 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 applicant has provided a declaration indicating that the product does not contain any substance of biological origin.

Control tests during production

Not applicable.

Control tests on the finished product

The proposed finished product specification at release is acceptable. The methods used are validated when necessary.

The specifications proposed at release are appropriate to control the quality of the finished product.

Stability

Results from stability studies with three production scale batches of the finished product for the 50 ml and the 100 ml pack sizes are available at long term conditions (25 °C/60% RH) for 24 months and accelerated conditions (40 °C/75% RH) for 6 months. Supportive stability data are given for three production scale batches of the already approved 20 mg/ml strength. The finished product is tested according to the specification at the end of shelf life.

The proposed finished product specification at the end of shelf life is acceptable.

Based on the stability data provided, extrapolation of long term data from 24 months up to 36 months is justified and the proposed shelf life of 3 years is considered acceptable.

In-use stability data are available for two batches of 50 and 100 ml each, stored under uncontrolled conditions (climatic zone 1) for 9 months and stored under long term conditions (25 °C/60% RH) for 36 months. Based on these results, an in-use shelf-life after first opening of the container of 28 days is considered acceptable.

The stability tests were performed in compliance with the respective the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) standards.

No photostability study was provided. Photostability testing should be conducted on at least one primary batch of the finished product according to the guideline on stability testing: Photostability testing of new veterinary drug substances and medicinal products (CVMP/VICH/901/00). However, taking into the account that the 20 mg/ml presentation is also packed in clear vials it is acceptable to omit the photostability study of the new strength (40 mg/ml).

The proposed in-use stability of 28 days is justified by the stability data provided.

Overall conclusions on quality

The data provided in part 2 of the dossier are in line with VICH and Ph. Eur. requirements and are acceptable. The product is a solution for injection which utilises standard pharmaceutical excipients. The proposed formulation for the 40 mg/ml strength has been satisfactorily justified and it has been shown that significant differences in the quality profile respect to the reference solution 20 mg/ml are not expected. The method of manufacture is a standard process and the specifications of the finished product

are satisfactory for the proposed composition and dosage form. The active substance is monographed in the Ph. Eur.; both active substance and the finished product are considered to be stable.

The composition of the new strength is justified and critical issues are discussed sufficiently.

Part 3 – Safety

A detailed and critical summary on the safety documentation is largely based on published scientific literature. The applicant has submitted a satisfactory dossier including peer-reviewed literature. Meloxicam is a well-known substance and has been used in veterinary medicines for many years and therefore this approach is considered acceptable.

The safety of the product has already been assessed by the CVMP during the initial marketing authorisation application and later variations and extension applications. Appropriate measures to ensure the safe use of the product are included in the product information.

User safety

The applicant has presented a user safety assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/543/03-Rev.1.

Identified relevant exposure scenarios were accidental self-injection and dermal exposure. The worst case scenario is accidental self-injection of 0.5 ml containing 20 mg of meloxicam which resulted in a calculated internal exposure level of 0.33 mg/kg for a 60 kg person. The margin of exposure (MOE) to the repeated dose no observed effect level (NOEL) is 0.6. For the dermal scenario a reasonable worst-case estimate is the spilling of one droplet of 50 microlitres containing 2 mg of meloxicam. Using a dermal bioavailability of 30%, the internal exposure was calculated to be 0.01 mg/kg for a 60 kg person. MOEs to the repeated dose NOEL were calculated to be 20 without gloves and 200 with gloves. It is expected that any professional using the product is aware of the user safety aspects of this product and follows good veterinary practice, which includes correct procedures for administration (e.g. wash hands). In humans a daily oral dose of 0.125 or 0.25 mg/kg bodyweight (bw)/day is recommended. Therefore, the risk for the professional women not pregnant or attempting to conceive is considered acceptable.

Meloxicam is considered to be maternotoxic/embryotoxic as observed from animal studies resulting in a lowest observed effect level (LOEL) of 0.125 mg/kg (maximum residue limit (MRL) summary reports, EMA). When considering the scenario of accidental self-injection a MOE of 0.4 (0.125/0.33) can be calculated. When considering the scenario of dermal exposure a MOE of 12.5 (0.125/0.01) or with gloves of 125 (0.125/0.001) can be calculated. Although the MOE when wearing gloves appears to be above 100, it should be noticed that this MOE was calculated using a LOEL without applying an additional safety factor (for extrapolation from a LO(A)EL to a NO(A)EL).

It cannot be excluded that some of the observed reproductive effects could also be induced by a single exposure. No risk reduction measures can limit the risk of accidental self-injection.

A risk of foetotoxic effects cannot be excluded.

When considering women of childbearing potential the exposure of 0.33 mg/kg is compared to the LOEL of 1 mg/kg/day derived from the fertility and early embryonic study in rats. A MOE based on a NO(A)EL could not be derived, but is considered to be definitely lower than 3, which is considered not acceptable. However, taking into account that the LOEL is derived from a repeated dose study whereas the accidental exposure is considered as a single exposure and with a low probability of occurrence, the inclusion of

following warning phrase in section 4.5 of the summary of product characteristics (SPC), is considered adequate to mitigate the risk for pregnant woman and woman attempting to conceive.

“In view of the risk of accidental self-injection and the known adverse class-effects of NSAIDs and other prostaglandin inhibitors on pregnancy and/or embryofoetal development, the veterinary medicinal product should not be administered by pregnant women or women attempting to conceive.”

The other user safety warnings in the already authorised strengths of Metacam solution for injection are appropriate for this strength and have been included in the SPC.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the VICH guideline GL6 on environmental impact assessment (EIAs) for veterinary medicinal products (VMPs) - Phase I (CVMP/VICH/592/98-FINAL). Given that the product is for the treatment of an individual or a small number of animals in a flock or herd, the environmental risk assessment can stop at Phase I.

Metacam 40 mg/ml solution for injection is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

A detailed and critical summary on the safety documentation is largely based on published scientific literature. The applicant has submitted a satisfactory dossier including peer-reviewed literature. Meloxicam is a well-known substance and has been used in veterinary medicines for many years and therefore this approach is considered acceptable. The new strength was formulated to be pharmaceutically identical to Metacam 20 mg/ml solution for injection and the dosing regimen will be the same, i.e. a single intravenous injection at a dosage of 0.5 mg meloxicam/kg bw and 0.6 mg meloxicam/kg bw in cattle and horses, respectively. It can be assumed that the safety profile for the target animal will be the same as for Metacam 20 mg/ml.

A user safety assessment was provided concluding on sufficient warnings and safety measures. As meloxicam is considered to be maternotoxic/embryotoxic a precautionary warning is included in section 4.5 of the SPC and other product information.

The environmental risk assessment can stop in Phase I. Metacam 40 mg/ml solution for injection is not expected to pose a risk for the environment when used according to the SPC.

Residues documentation

Residue studies

No new studies have been provided. This is considered acceptable.

Pharmacokinetics

No studies on pharmacokinetics were performed with Metacam 40 mg/ml solution for injection. This is considered acceptable.

Depletion of residues

No residue depletion studies were provided for Metacam 40 mg/ml. Given that the intravenous route of administration and the dosage regimen of Metacam 40 mg/ml solution are the same as for Metacam 20 mg/ml solution for injection it is considered that the difference in strength between the two formulations will have no influence on the depletion kinetics. Therefore the omission of residue depletion studies is considered acceptable. The same withdrawal period as for Metacam 20 mg/ml is considered justified.

MRLs

The active substance in Metacam is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010:

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

The excipients listed in section 6.1 of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Withdrawal periods

The new strength Metacam 40 mg/ml solution for injection is an extension application for Metacam. Metacam 40 mg/ml solution for injection will be administered intravenously as an aqueous solution to cattle and horses; the dosing regimen is the same as for Metacam 20 mg/ml, i.e. a single intravenous injection at a dosage of 0.5 mg meloxicam/kg bw and 0.6 mg meloxicam/kg bw in cattle and horses, respectively. Pharmacokinetics, depletion of residues and the maximum residue limits for Metacam 40 mg/ml solution for injection are considered identical to Metacam 20 mg/ml solution for injection. Therefore, it is considered acceptable to apply the same withdrawal period to Metacam 40 mg/ml as that established for Metacam 20 mg/ml.

Overall conclusions on the residues documentation

The proposed withdrawal periods as established for Metacam 20 mg/ml solution for injection are considered acceptable for the new strength Metacam 40 mg/ml solution for injection:

Cattle:

Meat and offal: 15 days, milk: 5 days.

Horses:

Meat and offal: 5 days.

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

Part 4 – Efficacy

This is an extension application to include a new strength 40 mg/ml solution for injection which is qualitatively the same and quantitatively similar to Metacam 20 mg/ml. No bioequivalence study was provided. According to the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-Rev.2) studies to compare the rate and extent of absorption between two formulations or products containing identical active substances are generally not required if both products fulfil one or more of the following conditions: The product is to be administered solely as an aqueous intravenous solution containing the same active substance as the currently approved product and both products contain the same excipients in very similar quantities and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance.

The lack of a bioequivalence study can be accepted as the conditions stated in section 7.1.a of the CVMP Guideline on bioequivalence studies (EMEA/CVMP/016/00-Rev.2) are considered fulfilled: The new strength 40 mg/ml is an aqueous intravenous solution which is qualitative the same to Metacam 20 mg/ml and differs only in the amount of the active substance and one excipient. Thus, bioequivalence can be assumed between the two formulations. Consequently, results from pharmacological or clinical tests are not required for the new strength 40 mg/ml solution for injection.

Target animal tolerance

The new strength of Metacam, 40 mg/ml solution for injection, is to be given solely intravenously to horses and cattle, as a single injection. Metacam 20 mg/ml solution for injection is currently authorised for the same route of administration. The dose recommendation for the new strength is the same as for the 20 mg/ml formulation, implying that the new strength will allow for the administration of a smaller volume. The applicant refers to the target animal safety guideline (VICH GL43) which mentions that if intravascular administration is the only route proposed, consideration should be given to the effect of extravascular administration of the veterinary medicinal product.

The applicant referred to bibliographic information to support tolerance in case of accidental extravascular administration.

Furthermore, meloxicam is used in the EU for more than ten years with recognised efficacy and an acceptable level of safety for the proposed indications in the target species using the proposed route of administration and dose regimen. It is also remarked by the applicant that the volume to be injected is only 50% of the volume that needs to be injected for the meloxicam 20 mg/ml which is approved for intravenous injection. Finally, it is mentioned that the only local irritation reported is in pigs in form of a sporadic slight lesion in muscle caused by the injected volume.

The CVMP considers that, in account of the fact that this new formulation will only be administered intravenously the only potential difference in safety profile as compared to the already approved 20 mg/ml solution for injection would be related to local tolerance. However, given that published data have demonstrated that Metacam is well tolerated when administered by different administration routes and that accidental extravasal administration would be a rare event likely concerning a small volume, it can be concluded that local safety would be sufficient for the 40 mg/ml solution for injection.

Overall conclusion on efficacy

This is an extension application to include a new strength 40 mg/ml solution for injection which is qualitatively the same to Metacam 20 mg/ml. No bioequivalence study was provided. The waiver of a bioequivalence study can be accepted as the conditions stated in section 7.1.a of the CVMP Guideline on bioequivalence studies (EMEA/CVMP/016/00-rev.2) are considered fulfilled: The new strength 40 mg/ml is an aqueous intravenous solution which is qualitative similar to the authorised Metacam 20 mg/ml and differs only in the amounts of the active substance and of one excipient. Thus, bioequivalence can be assumed between the two formulations and it can be expected the efficacy and clinical tolerance of Metacam 40 mg/ml will be the same as for Metacam 20 mg/ml when administered intravenously.

It is considered that accidental extravasal administration of the higher concentration of meloxicam would be a rare event likely concerning a small volume and published data have demonstrated that Metacam is well tolerated when administered via different administration routes. Thus, it can be concluded that local safety would be acceptable for the 40 mg/ml solution for injection.

Part 5 – Benefit-risk assessment

Introduction

This extension application for Metacam is to add a new strength 40 mg/ml suspension for injection for the existing target species cattle and horses. The product was developed to be essentially similar to the authorised presentation Metacam 20 mg/ml solution for injection.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

Benefit assessment

Direct therapeutic benefit

The therapeutic benefit assessment for the new strength remains the same as that established for Metacam 20 mg/ml solution for injection for cattle and horses already authorised.

The benefit of Metacam 40 mg/ml solution for injection would be its efficacy in the treatment of:

Cattle: For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs; for use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle; for adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy and for the relief of post-operative pain following dehorning in calves.

Horses: For use in the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders and for the relief of pain associated with equine colic.

Additional benefits

The volume of the solution for injection to be administered for Metacam 40 mg/ml will be 50% lower than the volume needed with a meloxicam 20 mg/ml solution for injection, providing an additional benefit for the treatment of larger animals.

Risk assessment

Quality:

The formulation and manufacture of Metacam 40 mg/ml solution for injection is well described and specifications set will ensure that product of consistent quality will be produced.

Following the re-audit of the active substance manufacturing site, the applicant is recommended to provide an updated QP declaration according to the Guidance for the template for the qualified person's declaration concerning GMP compliance of active substance manufacture (EMA/196292/2014).

For the target animals:

In conclusion, the new strength represents the same risks to target animals as those for Metacam 20 mg/ml when used in accordance with the SPC.

For the user:

A risk to pregnant women and women attempting to conceive was identified due to the embryotoxic and repro-toxic potential of meloxicam.

For the environment:

The product is not expected to pose any unacceptable risk to the environment when used as recommended.

For the consumer:

The dosing regimen of the new strength is the same as for Metacam 20 mg/ml solution for injection and the same withdrawal periods are considered acceptable.

It is accepted that the new strength will represent the same risks to consumers as those for Metacam 20 mg/ml when used in accordance with the SPC.

Risk management or mitigation measures

The same appropriate precautionary measures as for Metacam 20 mg/ml are included in the SPC and product information to prevent risks for the target animals, the user and for the environment.

In addition, a precautionary measure is included in section 4.5 of the SPC to prevent a risk to pregnant women and women attempting to conceive.

The same withdrawal periods as those of Metacam 20 mg/ml solution for injection can be applied to Metacam 40 mg/ml solution for injection to ensure the safety for the consumer.

Evaluation of the benefit-risk balance

Metacam 40 mg/ml solution for injection has been shown to have a positive benefit-risk balance overall.

The new strength is expected to be efficacious for the same indications as those already approved for Metacam 20 mg/ml solution for injection for cattle and horses.

The formulation and manufacture of Metacam 40 mg/ml solution for injection is well described and specifications set will ensure that product of consistent quality will be produced.

It is well tolerated by the target animals and does not present an unacceptable risk for users and the environment when used as recommended. Appropriate warnings are proposed in the SPC to this effect. A sufficient withdrawal period has been set.

Conclusion

Based on the original and complementary data presented the CVMP concluded that the quality, safety and efficacy of Metacam 40 mg/ml solution for injection for cattle and horses are considered to be in accordance with the requirements of Directive 2001/82/EC. The overall benefit-risk evaluation is deemed positive with sufficiently clear and complete product information.

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP recommends the extension of the marketing authorisation for Metacam to include Metacam 40 mg/ml solution for injection for cattle and horses.