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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a variation requiring assessment for Melovem (EMEA/V/C/000152/VRA/0015)

INN: Meloxicam

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

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Introduction

Submission of the variation application

In accordance with Article 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Dopharma Research B.V. (the applicant), submitted to the European Medicines Agency (the Agency) on 26 July 2022 an application for a variation requiring assessment for Melovem.

Rapporteur: Rory Breathnach

Co-rapporteur: Niels Christian Kyvsgaard

Scope of the variation

Melovem (meloxicam) is already authorised for use in cattle, horses and pigs for the following indications:

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.

Pigs: For use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation. For adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy.

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

Melovem is currently authorised as a solution for injection in concentrations of 5 mg/ml, 20 mg/ml and 30 mg/ml of meloxicam and is presented in vials of 100 mg for all strengths and in vials of 50 ml and 250 ml for the 20 and 30 mg/ml strengths.

Variation(s) requested	
I.II.1.e	I.II.1.e - Changes to strength, pharmaceutical form and route of administration - Change or addition of a new route of administration

The scope of this variation is to add a new pharmaceutical form and new strength, a 15 mg/ml oral suspension for horses, to the already existing marketing authorisation. This new presentation also introduces a new route of administration.

At the time of submission, the applicant applied for the following indication for the proposed new pharmaceutical form and strength:

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

This indication is already approved for horses in the existing marketing authorisation.

Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 2, Part 3, and Part 4

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided an updated summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF) with reference number PSMF-B6C60C83-A, has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

The active substance is manufactured outside of the EU by two manufacturers. Valid QP declarations were received from the Qualified Person (QP) at the EU batch release site for both manufacturers.

Batch release of the finished product takes place at Dopharma B.V., Raamsdonksveer, Netherlands. The site has a manufacturing authorisation issued on 25 August 2021 by the Netherlands. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for activities indicated above, has been provided.

Overall conclusions on administrative particulars

The summary of pharmacovigilance system master file was considered to be in line with legal requirements.

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

Part 2 - Quality

Composition

The product is an aqueous, yellow, oral suspension containing 15 mg/ml of the active substance meloxicam. The other ingredients include sodium benzoate (preservative), citric acid (acidifier), glycerol (flavouring agent), honey aroma (flavouring agent), hydroxyethylcellulose (suspending agent), colloidal anhydrous silica (suspending agent), saccharin sodium (flavouring agent), sorbitol (flavouring agent), xylitol (flavouring agent), and purified water.

It is packaged in white, rectangular high density polyethylene bottles with 250 ml or 500 ml of product and provided with a measuring syringe and in white, round high density polyethylene bottles with 100 ml of product packaged in acardboard box and provided with a measuring syringe.

Containers and closure system

The primary packaging is white, rectangular high density polyethylene bottles with 250 ml or 500 ml of product, closed with a white polypropylene screw cap with an EPE/PE liner, and provided with a polypropylene transparent lid with space to include a polypropylene measuring syringe with a synthetic rubber piston, and white, round high density polyethylene bottles with 100 ml of product closed with a white polypropylene screw cap with an EPE/PE liner, and a polypropylene measuring syringe with a synthetic rubber piston in a cardboard box. Justification of the choice of pack sizes has been provided, demonstrating that the pack sizes are consistent with the dosage regimen and duration of use. As part of the product development, studies were also carried out to establish the suitability of the dosing syringe provided with the finished product, and data has been provided to demonstrate the compliance of the product with the requirements of Ph. Eur. 2.9.27 'Uniformity and accuracy of delivered doses from multidose containers'.

Acceptable specifications have been provided for the bottles, liner and caps, and the measuring syringe. Declarations of the compliance of the bottles, liner, caps and syringe with EU Regulation No 10/2011, as amended have been provided, along with a declaration of the compliance of the rubber piston of the syringe with Ph. Eur. 3.2.2 'Plastic containers and closures for pharmaceutical use'.

Product development

Melovem was first authorised as a generic of Metacam and therefore Melovem 15 mg/ml oral suspension for horses was developed as a generic of the product Metacam 15 mg/ml oral suspension for horses. Formulation development was based on the information in the publicly-available SPC for the reference product.

The generic product contains the same quantitative composition of the active substance, with the same excipients with the exception of sodium dihydrogen phosphate dihydrate, which is not included in the generic product. The applicant has justified the omission of this excipient as not required for the maintenance of pH and stability of the product. The generic also has the same pharmaceutical form as the reference product. Tabulated batch analysis has been provided for one batch each of the reference and generic products demonstrating comparability for pH, density, and assay of the active substance and preservative, and comparative dissolution profiles have been provided for a batch of the reference product and a lab-scale batch of the proposed formulation. A bioequivalence study between the reference and proposed generic products has been provided, and comparative batch analysis data has been provided for a number of generic product batches to demonstrate that the generic product used in the bioequivalence study is representative of typical batches with respect to physico-chemical properties such as pH, density, viscosity and dissolution, related substances and assay of the active substance and preservatives.

The manufacturing process was developed based on lab-scale experiments, an international patent (WO 2006/061351 AI), and a production-scale placebo. An elemental impurities risk assessment was provided indicating that no elemental impurities are likely to be present at or above 30% of the ICH Q3D option 1 limit.

Description of the manufacturing method

The manufacturing process consists of the preparation of a suspension and a solution and subsequent mixing steps. The process is adequately described. Process validation data has been provided for three finished product batches of the proposed batch size. Compliant results are

provided for the proposed in-process controls, finished product release testing, and for content uniformity testing on ten samples were taken at regular intervals during filling. However, in line with the *Guideline on process validation for finished products – information and data to be provided in regulatory submission* EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1, the product is considered to be non-standard i.e. it is a suspension (specialised dosage form) and it contains an active substance present at a low content (<2% of the composition). As such, the batch size is restricted to that which has been validated, and confirmation has been provided that the product is filled immediately after manufacture and that there are no bulk hold times.

Control of starting materials

Active substance

The active substance meloxicam is monographed in the Ph. Eur. And data on the active substance is provided in the form of two Ph. Eur. Certificates of Suitability (CEPs), copies of which have been provided within the application. The relevant information has been assessed by the EDQM before issuing the Certificates of Suitability.

The active substance specification complies with the Ph. Eur. Monograph with tests for appearance, solubility, identification (IR), related substances (HPLC), loss on drying, sulphated ash and assay (HPLC). It also includes the additional requirements of the Ph. Eur. CEPs for residual solvents, along with a test and limit for particle size, and for polymorphic form.

However, the CEPs do not cover the micronised quality of the active substance, and so information has been provided on the manufacturing sites, and descriptions of the micronisation processes have been provided. In addition, it has been confirmed that the container closure system for the micronized active substance is the same as that of the active substance.

Acceptable justification has been provided for the proposed limits for particle size.

Acceptable comparative batch analysis data has been provided for 3 batches of the active substance from each of the manufacturers. The results are within the specifications and consistent from batch to batch, and between manufacturers. In addition, comparative data has been provided to demonstrate that the polymorphic form of the active substance from both manufacturers is the same as that of the active substance batch used in the manufacture of the batches of the finished product included in the bioequivalence studies.

Information on the reference standard has been provided.

Based on stability results the retest period of the micronised meloxicam is 60 months in the original packaging with the added temperature condition of store below 25^{o}C for one manufacturer.

Excipients

All excipients are well known pharmaceutical ingredients. Part 2.C.2 has been provided which includes reference to compliance of the pharmacopoeial excipients with the current edition of the European Pharmacopoeia.

The flavouring agent honey aroma is not monographed in a pharmacopoeia. The general composition of the honey aroma has been provided. Acceptable specifications have been provided for the excipient in line with the requirements of EMEA/CVMP/004/98-Final 'Note for guidance: excipients in the dossier for application for marketing authorisation for veterinary medicinal

products'. A declaration has been provided of the compliance of the honey aroma with Regulation EC No 1334/2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods, and Regulation No 1333/2008 on food additives.

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 (EMEA/410/01). 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 finished product release specification controls relevant parameters for the dosage form, including tests for appearance of the product and packaging, fill volume, pH (Ph. Eur.), relative density (Ph. Eur.), viscosity, redispersibility, dissolution, identification and assay of the active substance and of the preservative, related substances, and microbial quality (Ph. Eur.). The finished product specifications are considered to be acceptable.

The analytical methods are well described and have been validated in accordance with VICH GL1 *Validation of analytical procedures: definition and terminology* and GL2 *Validation of analytical procedures: methodology*.

Acceptable comparative batch analysis data has been provided for three production scale process validation batches. The results for all three batches comply with the proposed specifications and are comparable between batches, confirming the consistency of the manufacturing process and its ability to manufacture to the proposed product specification. Satisfactory information has been provided for the reference standards.

Stability

The proposed shelf-life of the veterinary medicinal product as packaged for sale is 3 years, with no special storage conditions. The proposed in-use shelf-life is 6 months, with storage below 25°C. The proposed shelf-life specification limits are the same as those for release.

Stability data is provided for three production scale batches of the finished product. Samples were stored at long-term conditions of 25°C/60% RH, intermediate conditions of 30°C/65% RH, and accelerated conditions of 40°C/75% RH. Confirmation has been provided that the stability protocol will be updated to include the 100 ml pack size in future stability studies.

The parameters monitored on stability are appearance of the product and packaging, pH, relative density, identification and assay of the active substance and of the preservative, and related substances. In addition, microbial testing is only to be performed at the initial and final (36 month) time-points on long-term conditions. VICH GL 3 compliant data has been provided to 30 months on long-term conditions of 25°C/60% RH and on intermediate conditions of 30°C/65% RH, and to 12 months on accelerated conditions of 40°C/75% RH.

No trending in assay of meloxicam is apparent, but significant variation is observed in the results.

Variation is also apparent for the assay of the preservative, but no trending is apparent with the exception of a decreasing trend observed for one batch in the 1000 ml pack size, on intermediate conditions. Very little variation is seen for pH and for relative density. All results for related substances (specified, unspecified and total) are 'none detected'. All results are within specification, for both pack sizes and on all storage conditions.

Statistical analysis has been applied to the stability data, indicating that no substantial degradation occurs for the meloxicam assay. For the preservative, the statistical analysis indicates that degradation of the preservative occurred at both long-term and intermediate conditions. The 95% confidence levels for meloxicam and for sodium benzoate remain within specification during the 30-month test periods for long-term and intermediate conditions and within specification for the 6 months required by VICH GL3 'Stability testing of new veterinary drug substances and medicinal products'.

In addition, satisfactory data has been provided for viscosity, redispersibility and dissolution testing on batches of up to 6 years. As such, the data provided supports the proposed shelf-life of 3 years with no special storage conditions.

An in-use stability study was performed on 2 batches of the finished product, stored for 9 months prior to testing, with testing on the 300 ml capacity bottles for both batches. The parameters monitored on in-use stability at all time-points are appearance of the product and packaging, assay of the active substance and of the preservative, and related substances. Instead of microbial testing, testing for efficacy of antimicrobial preservation was performed, in line with the requirements of Ph. Eur. 5.1.3, at the end of the study, on the remaining quantities of product in the containers. Identification of the active substance and of the preservative, pH and relative density were performed at the initial and final time-points only. Preservative efficacy testing of one of the batches was fully compliant with Ph. Eur. 5.1.3, requirements. All physico-chemical results were within specification and there was no evidence of changes over the course of the study performed (i.e. no trending of results, no decreases in assay, related substances results were 'none detected'). However, as the in-use study was not designed to mimic use of the product in practice, another in-use study protocol has been provided that is designed to simulate the use of the product in practice. Nevertheless, it is considered that the in-use data provided to date is sufficient to provide assurance that the product does not pose a risk regarding the approval of an in-use shelf-life of 6 months. The applicant is recommended to provide the results of the additional in-use stability study as soon as available by way of a VRA. In addition, a declaration has provided that the study will also be performed on a batch at the end-of-shelf-life.

A photostability study has also been provided, demonstrating that no warnings regarding photosensitivity are required for the product.

Overall conclusions on quality

The product is an aqueous oral suspension containing 15 mg/ml of the active substance meloxicam, and 1.5 mg/ml of sodium benzoate as a preservative. It is packaged in white, high density polyethylene bottles with 100 ml, 250 ml or 500 ml of product, closed with a white polypropylene screw cap, and provided with a measuring syringe.

Information on the development, manufacture and control of the active substance and the finished product is considered to be satisfactory.

In the product development section, the applicant provides a summary of the development of the formulation and of the manufacturing process. Physicochemical aspects relevant to the performance

of the product have been investigated. Justification of the choice of pack sizes has been provided, along with data to demonstrate the compliance of the product with the requirements of Ph. Eur. 2.9.27 'Uniformity and accuracy of delivered doses from multidose containers'. An acceptable elemental impurities risk assessment has been provided.

Process validation data has been provided for three finished product batches of the minimum proposed batch size. Given that the product is considered to be non-standard, the batch size is restricted to the size that has been validated.

The active substance meloxicam is monographed in the Ph. Eur. and data on the active substance is provided in the form of Ph. Eur. Certificates of Suitability (CEPs). In addition, information has been provided on the manufacturing sites of the micronisation process, the micronisation processes, the container closure system and retest period of the micronized active substance. Acceptable comparative batch analysis data has been provided, along with comparative data on the polymorphic form. Information on the reference standard has been provided.

Compliance with the current Ph. Eur. monographs for the pharmacopoeial excipients is detailed. Acceptable specifications have been provided for the non-pharmacopoeial honey aroma, along with declarations of its compliance with EU flavouring regulations. Information on the container-closure systems for the active substance is provided in the Ph. Eur. CEPs. Acceptable specifications have been provided for the finished product container-closure components. Declarations of the compliance of the packaging components with EU Regulation No 10/2011 as amended, or with the relevant Ph. Eur. monograph has been provided. Data has been presented to give reassurance on TSE safety.

The finished product release specification controls relevant parameters for the dosage form. Analytical methods and validation have been provided. Acceptable comparative batch analysis data has been provided, along with information on the reference standards.

Information on the stability of the active substance is provided in the Ph. Eur. CEPs. For the finished product, VICH GL 3 compliant data has been provided along with satisfactory data has been provided for viscosity, redispersibility and dissolution testing on batches of up to 6 years. The data supports the proposed shelf-life of 3 years with no special storage conditions. Acceptable data has been provided to support the proposed 6 month in-use shelf life. A photostability study has also been provided, demonstrating that no photo-sensitivity warnings are required for the product.

Therefore, all outstanding issue have been addressed by the applicant and it can be concluded that the product is of satisfactory quality.

Part 3 – Safety documentation (Safety and residues tests)

The scope of this variation requiring assessment is to add a new pharmaceutical form and new strength, i.e. a 15 mg/ml oral suspension for horses, to the already existing marketing authorisation for Melovem. This presentation also introduces a new route of administration.

At the time of submission, the applicant applied for the following indication for the proposed new pharmaceutical form and strength:

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

This indication is already approved for horses in the existing marketing authorisation.

Melovem was first authorised on 7 July 2009 as a generic of Metacam. Therefore, the reference product cited for this variation is Metacam 15 mg/ml oral suspension for horses (EU/2/97/004/009, EU/2/97/004/030).

Safety tests

In this application, comparative bioavailability between the reference product and Melovem 15 mg/ml oral suspension for horses has been investigated by means of an *in vivo* bioequivalence study, and bioequivalence is claimed.

It is accepted that, based on the published SPC of the reference product, Melovem 15 mg/ml oral suspension for horses and the reference product are qualitatively and quantitatively the same in respect to the active substance, meloxicam, and are qualitatively similar in respect to the excipients. Furthermore, Melovem 15 mg/ml oral suspension for horses is of the same pharmaceutical form (suspension) and is intended for use in the same manner (oral administration) to the same target species (horses) for the same indications and at the same recommended dose (0.6 mg/kg bodyweight once daily) as the reference product.

Pharmacology

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 4.

Toxicology

No data relating to the toxicological profile of the product have been provided, as bioequivalence with the reference product has been claimed. Given the fact that Melovem 15 mg/ml oral suspension for horses and the reference product contain the same concentration of active substance (meloxicam) and the excipients are qualitatively similar, the omission of toxicological data is acceptable.

Other requirements

Special studies

No data were presented, as bioequivalence with the reference product has been claimed. Given the fact that Melovem 15 mg/ml oral suspension for horses and the reference product contain the same concentration of active substance (meloxicam), and the excipients are qualitatively similar, the omission of results of irritation, immunotoxicity and sensitisation studies can be accepted.

Observations in humans

No data were presented.

Excipients

No data were presented. However, based upon the SPC of the reference product, it can be accepted that the candidate and reference formulations are qualitatively similar in respect to the excipients, and none of the excipients are considered to represent a safety concern.

User safety

A user safety assessment conducted broadly in accordance with the CVMP "Guideline on user safety for pharmaceutical veterinary medicinal products" (EMA/CVMP/543/03) was provided. It is accepted that Melovem 15 mg/ml oral suspension for horses and the reference product are of the same pharmaceutical form (suspension) and are intended for use in the same manner (oral administration) in the same target species (horses) at the same recommended dose. Furthermore, Melovem 15 mg/ml oral suspension for horses and the reference product are qualitatively and quantitatively the same in respect to the active substance, meloxicam, and are qualitatively similar in respect to the excipients. Consequently, no difference in exposure of the user to the final formulation of Melovem 15 mg/ml oral suspension for horses when compared to the reference product is anticipated.

Considering the above, the CVMP concludes that the risk posed to the user by Melovem 15 mg/ml oral suspension for horses is not expected to differ from that posed by the reference product. The same user safety warnings as approved by the CVMP for the reference product have been proposed for Melovem 15 mg/ml oral suspension for horses, and this is considered appropriate. Provided the product is stored, handled, administered and disposed of in accordance with the recommendations included in the proposed SPC, it is accepted that Melovem 15 mg/ml oral suspension for horses will not present an unacceptable risk to the user.

Environmental risk assessment

An environmental risk assessment (ERA) according to the relevant guideline (VICH GL 6) was provided. The environmental risk assessment can stop in phase I and no phase II assessment is required because (i) the veterinary medicinal product is intended to be used for a limited market in a species that is reared and treated similarly to a species for which an environmental risk assessment already exists; and (ii) the veterinary medicinal product will be used to treat a small number of animals in a flock or herd.

As is the case for the reference product, no specific environmental warnings are considered necessary and the standard text relating to disposal of unused product is proposed for inclusion in the SPC of Melovem 15 mg/ml oral suspension for horses, and this is considered acceptable.

Melovem 15 mg/ml oral suspension for horses is not expected to pose a risk for the environment when handled, used, stored and disposed of according to the SPC.

Residue tests

MRL status

The active substance in Melovem 15 mg/ml oral suspension for horses (meloxicam) is an allowed substance listed in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmaco-logically 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) 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 veterinary medicinal product.

Depletion of residues

No data were provided.

Residue analytical method

No data were provided.

Withdrawal periods

Based on the CVMP "Guideline on determination of withdrawal periods for edible tissues" (EMA/CVMP/SWP/735325/2012), which defines the circumstances in which the withdrawal period of a reference product can be extrapolated to a bioequivalent generic product, the withdrawal period as approved for the reference product has been extrapolated to Melovem 15 mg/ml oral suspension for horses, i.e. "Meat and offal: 3 days".

In respect of the bioequivalence study provided in support of the current application, the calculated lower and upper confidence limits for meloxicam were 102 and 110% for AUC_{last} and 86 and 128% for C_{max}. Therefore, equivalence in terms of AUC can be accepted. As the 90% confidence interval for the ratio for C_{max} is greater than 125% (128%) (please also refer to the assessment of the in vivo bioequivalence study in part 4), further reassurance of adequate consumer safety is required if the withdrawal period of 3 days for meat and offal is to be extrapolated from the reference product to the candidate product. On this point, the following publicly available information is noted:

- In a residue depletion study conducted with the reference product, Metacam 15 mg/ml oral suspension for horses, residues were less than the limit of quantification (LOQ) in muscle from 24 hours, and less than the LOQ in liver from 48 hours. While residues were marginally above the MRL in 2 of 4 kidney samples at 48 hours, the withdrawal period was calculated to be 58.4 hours using the statistical approach (rounded up to 72 hours or 3 days). Based on these data (available in the EPAR for Metacam15 mg/ml oral suspension for horses), it is accepted that a "buffer" is in place that can compensate for the minor excursion above the upper acceptance limit for C_{max} in the case of the candidate product (whose qualitative composition is very similar to that of the reference product, except for one excipient that is not included in the candidate product).

In the present case, the upper acceptance limit of 125% is marginally breached for C_{max} only, but the 90% confidence intervals for this parameter are fully contained within the wider limits of 70-143%. Considering all available information, it is accepted that the proposed 3-day withdrawal period is adequate and that a confirmatory residue depletion study is not required.

Overall conclusions on the safety documentation: safety and residues tests

This VRA is to add a new pharmaceutical form and strength, i.e. a 15 mg/ml oral suspension for horses, to the already existing marketing authorisation for Melovem. A suitable reference product has been cited (Metacam 15 mg/ml oral solution for horses) and bioequivalence between the reference product and Melovem 15 mg/ml oral suspension for horses has been investigated by means of an in vivo bioequivalence study.

It is accepted, based on the published SPC of the reference product, that Melovem 15 mg/ml oral suspension for horses and the reference product are qualitatively and quantitatively the same in respect to the active substance, meloxicam, and are qualitatively similar in respect to the excipients. Furthermore, Melovem 15 mg/ml oral suspension for horses is of the same pharmaceutical form (suspension) and is intended for use in the same manner (oral administration) in the same target species (horses) for the same indications and at the same recommended dose as the reference product.

Toxicology:

No data relating to the toxicological profile of the product have been provided, as bioequivalence with the reference product has been claimed. Based on the results of the in vivo bioequivalence study and given the fact that Melovem 15 mg/ml oral suspension for horses and the reference product contain the same concentration of active substance (meloxicam), and the excipients are qualitatively similar, the omission of toxicological data is considered acceptable.

User safety:

A user safety assessment broadly in line with the relevant guidance document has been presented. Based on the similarities between Melovem 15 mg/ml oral suspension for horses and the reference product as outlined above, no difference in exposure of the user to the final formulation of Melovem 15 mg/ml oral suspension for horses when compared to the reference product is anticipated.

The risk posed to the user by Melovem 15 mg/ml oral suspension for horses is not expected to differ to that posed by the reference product. The same user safety warnings as approved by the CVMP for the reference product have been proposed for Melovem 15 mg/ml oral suspension for horses and this is considered appropriate. Provided the product is stored, handled, administered, and disposed of in accordance with the recommendations included in the proposed SPC, it can be accepted that Melovem 15 mg/ml oral suspension for horses will not present an unacceptable risk to the user.

Environmental risk assessment:

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the SPC.

Withdrawal periods:

A withdrawal period for meat and offal of 3 days has been proposed for Melovem 15 mg/ml oral suspension for horses (as extrapolated from the withdrawal period as approved for the reference product), and is accepted.

Part 4 – Efficacy

This variation is to add a new pharmaceutical form and new strength (i.e. a 15 mg/ml oral suspension for horses) to the already existing marketing authorisation for Melovem. This variation also introduces a new route of administration (i.e. oral administration).

The applicant applied for the following indication for the proposed new pharmaceutical form and strength:

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

This indication is already approved for horses in the existing marketing authorisation of Melovem 20mg/ml solution for injection.

Melovem was first authorised on 7 July 2009 as a generic of Metacam. Therefore, the reference product cited for this variation is Metacam 15 mg/ml oral suspension for horses (EU/2/97/004/009, EU/2/97/004/030).

Pre-clinical studies

Pharmacology

Pharmacodynamics

No pharmacodynamic studies were presented, and as the results of the *in vivo* bioequivalence study are considered acceptable, the omission of pharmacodynamic data is considered acceptable.

The pharmacodynamic properties of the active substance are detailed in section 5.1 of the SPC and based on those approved for the reference product.

Pharmacokinetics

An *in vivo* bioequivalence study in the target animal species, horses, was provided in which bioequivalence between Melovem 15 mg/ml oral suspension for horses and the reference product was investigated. Based upon the results of that study, bioequivalence between Melovem 15 mg/ml oral suspension for horses and the reference product is claimed. The pharmacokinetic properties of the active substance are detailed in section 5.2 of the SPC and are identical to those approved for the reference product.

Bioequivalence study

One *in vivo* GLP-compliant bioequivalence study, conducted largely in accordance with current guidance (Guideline on the conduct of bioequivalence studies for veterinary medicinal products, EMA/CVMP/016/2000-Rev.4), was provided. The purpose of the study was to demonstrate bioequivalence between the reference veterinary medicinal product and the generic candidate product, Melovem 15 mg/ml oral suspension for horses, at the recommended oral dose of 0.6 mg/kg bodyweight. The final formulation intended for marketing was used in the study.

A two-period, two-sequence single dose crossover study was performed with a sufficiently long wash-out period. The highest recommended dose according to the SPC of the reference product was used in the study, and the products were administered in accordance with the SPC of the reference

product. The number (n = 14) of study animals used was appropriately justified and the animals were clinically healthy and representative of the target animal species population. The animals were randomly assigned to one of two groups that were balanced for sex and bodyweight.

The evaluation of bioequivalence was based upon measurement of the active substance meloxicam in plasma, which is appropriate and in keeping with current guidance. The sampling schedule was also appropriate, and no animals or data points were excluded from the analysis.

Summary table of results of the bioequivalence study of meloxicam oral suspension in horses (fed).

Parameter	Test article	Reference article
C_{max} mean ± SD (µg/ml)	1.4216 ± 0.71422	1.2857 ± 0.54578
T_{max} median [range](h)	2.525 [0.51667 – 23.967]	2.275 [0.51667 – 11.767]
AUC_{last} mean ± SD (h. µg/ml)	11.186 ± 4.7764	10.526 ± 4.3754

The applicant specified *a-priori* in the study protocol that bioequivalence may be concluded if the 90% confidence intervals (CI) for the ratio of the means of the parameter AUC_{last} are included within the interval 80 - 125%, and if the 90% confidence intervals for the ratio of the means of the parameter C_{max} are included within the interval 70 - 143%.

The results of this study indicate that the 90% confidence intervals for the least-square mean differences (Test-Reference) of the ln-transformed means for both pivotal pharmacokinetic parameters lie within the pre-specified limits.

90% confidence intervals for the ratio of the geometric means of test and reference items

Parameter	Ratio of geometric means T/R	Lower Limit of 90% CI	Upper Limit of 90% CI
AUC_{last}	1.06	102 %	110 %
C_{max}	1.05	86 %	128 %

In considering whether the findings for the pharmacokinetic parameter C_{max} will impact on safety and efficacy of the candidate product, information from the public domain regarding other, centrally authorised meloxicam-containing oral presentations for horses were considered by the CVMP, and the following conclusions were reached:

Although bioequivalence with the reference product within the standard bounds of 80 – 125% has not been demonstrated in respect of C_{max}, when the known safety profile of orally administered meloxicam in horses is considered, it is accepted that the slight breaching of the upper 90% confidence interval limit as presented in this study does not present a clinically significant risk to the consumer, or to the target animal (see also section target animal safety, below).

Equivalence between candidate and reference products in respect of AUC is accepted as the upper and lower 90% confidence intervals lie within the standard bounds of 80 – 125%. Therefore, it is also accepted by the CVMP that based on the AUC data from the study provided, a similar efficacy profile to that of the reference product can be extrapolated to the candidate product.

In summary, the CVMP considers the results of the *in vivo* bioequivalence study provided adequate to permit extrapolation of the accepted safety and efficacy profiles of the reference product to the candidate product.

Based on the results of the study performed to validate the UPLC-MS/MS method used to quantify meloxicam in equine plasma, the method has been suitably validated, and sample stability for a period in excess of the maximum time between sample collection and analysis was also suitably verified.

Dose determination and confirmation

Dose justification

No data were presented; however, given that bioequivalence with a suitable reference product has been claimed, and the proposed posology for the candidate product is the same as that of the reference product, the omission of dose determination and confirmation data is considered acceptable. The same recommended dose as that already approved for the reference product has been proposed for section 4.9 of the SPC, which is considered acceptable.

Tolerance in the target animal species

No data were presented. The candidate and reference formulations are of the same pharmaceutical form (suspension) and are intended for use in the route of administration (orally) in the same target species (horses) for the same indications and at the same recommended dose.

In respect of the bioequivalence study, equivalence of AUC can be accepted. However, as the upper limit for the standard confidence interval of 125% for C_{max} is breached (128%), further reassurance that this result will not have a significant impact on target animal safety, would be required.

On this point, it is noted that for the reference product, Metacam 15 mg/ml oral suspension for horses, an acceptable safety profile was established based on *in vivo* target animal tolerance studies. The following excerpt from the EPAR for Metacam is noted: *"Horses treated with the recommended dose for up to 42 days showed no clinical signs and no abnormalities were found at autopsy. After three to five times the recommended dose for 3 times the recommended treatment period, the animals showed typical signs of NSAID toxicity: loss of body weight, oedema, and ulcerations of the mucosa of the gastrointestinal tract and papillary necrosis of the kidney."*

These data are considered particularly relevant in the context of the reference product and the candidate product having the same qualitative and quantitative composition in terms of the active substance (meloxicam) and a qualitatively similar excipient profile (noting that that sodium dihydrogen phosphate dihydrate is included as an excipient in the reference product only).

Based on the above points, although bioequivalence with the reference product has not been demonstrated in respect of C_{max}, when the known safety profile of orally administered meloxicam in horses is considered, the CVMP agreed that the slight breaching of the upper 90% confidence interval limit as presented in this study does not present a clinically significant risk to the target animal.

Based on all available information, the omission of target animal tolerance data can be accepted.

Clinical trial(s)

No clinical data have been provided by the applicant. Based on the acceptability of the results of the *in vivo* bioequivalence study, noting in particular that the upper and lower 90% confidence intervals for AUC lie within the standard bounds of 80 – 125%, efficacy is expected to be the same for both

products when administered by the same routes and at the same recommended dose. As such, omission of clinical data is considered acceptable.

Overall conclusions on efficacy

An *in vivo* bioequivalence study that was conducted to GLP standard and designed largely in accordance with current guidance (Guideline on the conduct of bioequivalence studies for veterinary medicinal products, EMA/CVMP/016/2000-Rev.4) was provided. The purpose of this study was to demonstrate bioequivalence between the reference product and the generic product Melovem 15 mg/ml oral suspension for horses when administered at the recommended treatment dose of 0.6 mg meloxicam/kg bw.

The applicant specified *a-priori* that bioequivalence may be concluded if the 90% confidence intervals for the ratio of the means of the parameter AUC_{last} are included within the interval 80 - 125%, and if the 90% confidence intervals for the ratio of the means of the parameter C_{max} are included within the interval 70 - 143%. The results of this study indicate that the 90% confidence intervals for the least-square mean differences (Test-Reference) of the ln-transformed means for both pivotal pharmacokinetic parameters lie within the pre-specified limits. In considering whether widened acceptance criteria for the pharmacokinetic parameter C_{max} are acceptable and will not impact on safety and efficacy of the candidate product, information from the public domain regarding other, centrally authorised meloxicam-containing oral presentations for horses were considered by the CVMP and it is concluded that the results of the *in vivo* bioequivalence study provided are adequate to permit extrapolation of the accepted safety and efficacy profiles of the reference product to the candidate product.

The UPLC-MS/MS method used to quantify meloxicam in equine plasma has been suitably validated, and sample stability for a period in excess of the maximum time between sample collection and analysis was suitably verified.

As bioequivalence between the proposed generic product and the reference product has been claimed and based on the acceptability of the results of the *in vivo* bioequivalence study, the omission of pharmacodynamic data, dose determination, tolerance and clinical data is considered acceptable.

Part 5 – Benefit-risk assessment

Introduction

Melovem (meloxicam) is already authorised for use in cattle, horses and pigs for the following indications:

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.

Pigs: For use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation. For adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy.

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

Melovem solution for injection is presented in 3 strengths- 5 mg/ml, 20 mg/ml and 30 mg/ml and presented in vials of 100 ml for all strengths and additional vial sizes of 50 ml and 250 ml of the 20 and 30 mg/ml strengths.

The proposed variation is to add a new pharmaceutical form and strength - a 15 mg/ml oral suspension for horses. This new presentation will introduce a new route of administration – i.e. oral administration. The indication for the oral suspension is for the alleviation and relief of pain in both acute and chronic musculo-skeletal disorders in horses. This indication is already approved for horses for the solution for injection.

The application has been submitted in accordance with Article 62 of Regulation (EU) 2019/6.

Benefit assessment

Direct benefit

The proposed benefit of Melovem 15 mg/ml oral suspension for horses is its efficacy in alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses. The evidence for this is considered established based on claimed bioequivalence with the reference product when administered at the same recommended dose and interval, and via the same route of administration as recommended in the marketing authorisation of the reference product. As bioequivalence with the reference product is accepted, Melovem 15 mg/ml oral suspension for horses is expected to be as efficacious as the reference product.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner, in general. 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

The risks associated with the use of Melovem 15 mg/ml oral suspension for horses are expected to be the same as those associated with the reference product. Therefore, Melovem is not expected to present an unacceptable risk to the target animal, consumer, user, or environment when used as recommended and in accordance with the SPC.

Risk for the consumer

A withdrawal period of 3 days for meat and offal is proposed for the use of Melovem in horses. The product is not authorised for use in animals producing milk for human consumption.

Risk management or mitigation measures

Based on demonstration of bioequivalence, it is considered appropriate that the warnings and risk mitigation measures proposed for inclusion in the candidate product SPC reflect those approved for

the reference product. 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.

For comprehensive pharmacovigilance surveillance the frequency of submission of the results and outcomes of the signal management process, including conclusion on the benefit-risk balance shall be recorded in the pharmacovigilance database according to the frequency determined for the reference product (Metacam 15 mg/ml oral suspension for horses).

Evaluation of the benefit-risk balance

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, the environment and consumers, when used as recommended. Appropriate precautionary measures, including the same withdrawal periods as for the reference product, 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 supplementary data presented, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for a variation to the terms of the marketing authorisation for Melovem 15 mg/ml oral suspension for horses 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.