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Committee for Medicinal Products for Veterinary Use

CVMP Assessment Report for Melovem (EMEA/V/C/000152/X/003)

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

An application for an extension to the Community marketing authorisation for Melovem has been submitted by Dopharma Research B.V. to the European Medicines Agency (the Agency) on 26 September 2012 in accordance with Article 19 of Commission Regulation (EC) No. 1234/2008 and Annex I thereof.

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

Melovem 5 mg/ml solution for injection for cattle and pigs was granted a marketing authorisation by the European Commission on 07 July 2009.

This extension application is to add a new strength meloxicam 20 mg/ml solution for injection for cattle, pigs and horses. The reference product is Metacam 20 mg/ml solution for injection for cattle, pigs and horses.

The target species are cattle, pigs and horses. The route of administration of the new strength is subcutaneous and intravenous use in cattle, intramuscular use in pigs and intravenous use in horses.

The applicant applied for the following 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.

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.

The proposed withdrawal periods for meat and offal are 15 days in cattle, 5 days in pigs and horses and 5 days for milk (cattle).

Melovem 20 mg/ml solution for injection is presented in packs of 1 vial of 50 ml, 100 ml and 250 ml.

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

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system) which fulfils the requirements of Directive 2001/82/EC, as amended. 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

Declarations of compliance of the manufacture of the active substance with EU GMP requirements have been provided.

The finished product manufacturing sites involved in the manufacturing of Melovem 20 mg/ml solution are appropriately authorised and relevant GMP certificates are provided.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the dosage form manufacturing sites are considered in line with legal requirements.

Part 2 - Quality

Composition

Melovem 20 mg/ml solution for injection has been formulated to be essentially similar to Metacam 20 mg/ml solution for injection. Melovem 20 mg/ml solution for injection contains the same active substance (meloxicam) and preservative (ethanol) in the same concentration as the reference product. The formulation also includes the following excipients which are also present in the reference product: glycine, hydrochloric acid, sodium hydroxide, macrogol 300, meglumine, poloxamer 188 and water for injections. The difference in the formulation compared to the reference product is the replacement of disodium edetate by sodium citrate.

Container

The product is presented in colourless type I glass vials of 50, 100 and 250 ml with bromobutyl rubber closures and aluminium overseals. The glass vials are individually packaged within a cardboard box.

Development pharmaceutics

The formulation of the generic product was developed to be essentially similar to that of the reference product, except that disodium edetate was replaced with sodium citrate. Both sequestering agents have similar properties and this difference in excipients is not expected to have an impact on the bioavailability of the active substance. The selected concentration of sodium citrate is within the range specified for use as a sequestering agent in the Handbook of Pharmaceutical Excipients, Rowe R.C. et al 2006. The impurity profiles of the generic and reference products were shown to be similar. Data demonstrating compliance with the requirements of the European Pharmacopoeia (Ph. Eur.) test for fragmentation and self-sealing modified to use the maximum number of punctures expected in relation to the target species, dose and route of administration (using the appropriate needle size for that scenario) were provided.

Method of manufacture

The manufacturing process is a standard one involving sequential addition of the components to a portion of water with mixing conducted after each addition. Process validation has been conducted on pilot scale batches and an agreement to perform validation on three full scale batches post authorisation to the same validation protocol is included in the dossier.

Control of starting materials

Active substance

Meloxicam is described in a Ph. Eur. monograph and is supported by certificates of suitability issued by EDQM to both suppliers. Batch data are presented from each supplier. The data demonstrates full compliance with the Ph. Eur. monograph and the additional tests listed on the certificates of suitability. As the active substance is in solution in the product, functionality related parameters such as particle size and polymorphism are not relevant for this dosage form. One of the certificates of suitability for meloxicam include a 3 year retest period when stored in double polyethylene bags placed in fibreboard drums. Stability data for meloxicam from the second supplier is provided to support a retest period of 60 months in the proposed pack.

Excipients

All excipients (ethanol, glycine, hydrochloric acid, sodium hydroxide, macrogol 300, meglumine, poloxamer 188) comply with their respective Ph. Eur. monographs. Specifications and batch analysis are provided for each excipient.

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

None of the starting materials used for the active pharmaceutical ingredient 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).

Control tests during production

In-process controls are specified in the description of the manufacturing process, on the flow chart and as a separate table in the dossier. They are considered appropriate for the dosage form.

Control tests on the finished product

The specifications proposed at release and at the end of shelf-life are appropriate to control the quality of the finished product. The active substance is controlled to within +/-5% and the preservative to within +/- 10% in line with requirements. Diode array detection is used in the HPLC method for assay and a second identification test is not therefore required. Limits for individual related substances are just slightly wider than the limits for the active substance and well below VICH qualification thresholds. The limit for unspecified impurities is also below the VICH qualification threshold. Other tests on the specification are standard pharmacopoeial tests for the dosage form. Satisfactory validation of the analytical methods has been provided and is acceptable.

Stability

Stability studies were performed on pilot scale batches. The applicant intends to place the first three production scale batches on stability at long term conditions for the duration of the shelf life and at accelerated conditions for 6 months. Vials were stored in an inverted position at all storage conditions. 18 month data is currently available at 25 °C/60% RH, 30 °C/65% RH and 40 °C/75% RH. The real time studies are on-going until 36 months. The data demonstrate the product to be stable. The data is

considered sufficient to support (by extrapolation) the proposed shelf life of 30 months with no specific temperature storage precautions.

The photostability study showed that the product is photo labile. Samples stored in the outer pack were also exposed to light and no adverse trends were observed in these samples demonstrating that the outer pack provides adequate protection from light. Therefore the statement 'Keep the container in the outer carton in order to protect from light' is included in the product information.

A freeze/thaw study showed that the product is sensitive to freezing. Therefore the statements 'Do not refrigerate or freeze. Protect from frost' are included in the product literature.

An in-use stability test was conducted in support of the shelf life after first opening of 28 days. Preservative efficacy was conducted in accordance with Ph. Eur. 5.1.3 and the 'A criteria' met in all cases. The proposed in-use shelf-life of 28 days after first opening the immediate package is acceptable. The applicant will repeat the in-use study on a batch of product at the end of shelf life.

Overall conclusions on quality

The formulation is a simple solution for injection. Its formulation development, manufacture, control and stability are well described in the dossier and are acceptable. The quality data is in accordance with current requirements. CVMP/VICH guidelines have been taken into account and no significant deviations from current guidelines have been identified.

Shelf-life and storage precautions supported by the stability studies:

Shelf life of the veterinary medicinal product as packaged for sale: 30 months.

Shelf life after first opening the immediate packaging: 28 days.

Keep the container in the outer carton in order to protect from light.

Do not refrigerate or freeze. Protect from frost.

Part 3 – Safety

The data for this application are provided in accordance with Article 13(1)(a)(iii) of Directive 2001/82/EC (generic application).

An exemption from the requirement to provide in vivo bioequivalence data was claimed, on the basis that the veterinary medicinal product:

- has the same pharmaceutical form (solution for injection) as the reference product,
- will be administered parenterally as a solution,
- contains the same active substance in the same concentration as the reference veterinary medicinal product and the same excipients with one minor difference. The difference in excipients will have no impact on bioavailability.

Data presented in the dossier show that the formulation of Melovem 20 mg/ml is identical to that of the reference product Metacam 20 mg/ml with one exception: disodium edetate present in the reference product Metacam 20 mg/ml is replaced with sodium citrate. The applicant illustrated the similarity of Melovem and the reference product by referring to the authorised SPC of the reference product and by analytical verification.

Based on the information provided, the omission of bioequivalence studies can be accepted in accordance with paragraph 7(1)(b) of the CVMP Guidelines for the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-Rev.2).

Given that bioequivalence of Melovem 20 mg/ml solution for injection with the reference product was accepted, CVMP considered that no data in respect of pharmacology or toxicology are required.

User safety

A user safety assessment in accordance with CVMP guideline EMEA/CVMP/543/03-FINAL-Rev.1 was not provided. CVMP considered this being acceptable given that this application refers to Article 13(1) (a generic application) and that Melovem 20 mg/ml is considered bioequivalent with the reference product and that the minor difference in excipients does not constitute a risk to the user. Therefore it can be assumed that the new strength will pose the same risks to the user as the reference product.

The following same user safety statements as for the reference product are included in section 4.5 of the SPC:

- Accidental self-injection may give rise to pain. People with known hypersensitivity to NSAID should avoid contact with the veterinary medicinal product.
- In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Environmental risk assessment

A Phase I environmental risk assessment was provided in line with line with the VICH guideline GL6 - 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. Melovem 20 mg/ml solution for injection is not expected to pose a risk for the environment when used according to the SPC.

Residues documentation

No residue depletion studies were submitted in support of this application. Information has been provided by the applicant to demonstrate the similarity in formulations between Melovem 20 mg/ml solution for injection and the reference medicinal product, Metacam 20 mg/ml solution for injection.

Depletion of residues

Based on the information provided, CVMP accepted that the minor difference between the product and the reference product with respect to excipients is unlikely to have any effect on the depletion of residues from the injection site. Under these circumstances, it was agreed that the omission of residue depletion studies was justified.

MRLs

The active substance in Melovem 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-steroidalanti-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 product.

Withdrawal periods

The CVMP agreed that the same withdrawal periods as authorised for the reference product Metacam 20 mg/ml solution for injection are applicable to Melovem 20 mg/ml solution for injection:

Cattle: Meat and offal: 15 days; Milk: 5 days.

Pigs: Meat and offal: 5 days.

Horses: Meat and offal: 5 days.
Not authorised for use in horses producing milk for human consumption.

Part 4 – Efficacy

See also Part 3 of this report.

Given that bioequivalence of Melovem 20 mg/ml with the reference product is accepted, CVMP considers that Melovem 20 mg/ml will have the same efficacy profile as the reference product and therefore no efficacy data are required for Melovem 20 mg/ml solution for injection.

No target animal safety data has been provided in support of the application. However, given that:

- Melovem 20 mg/ml is considered identical in formulation to the reference product, with one minor exception (1 mg/ml of disodium edetate, present in the reference product Metacam 20 mg/ml, is replaced with 20 mg/ml sodium citrate), and
- the veterinary medicinal product is intended to be used in exactly the same way as the reference product,

the absence of target animal safety data can be accepted. It is considered appropriate that sections 4.6 and 4.10 of the SPC of Melovem 20 mg/ml include the same text as in the SPC of the reference product.

Part 5 – Benefit-risk assessment

Introduction

Melovem 20 mg/ml solution for injection in cattle, pigs and horses is an extension application to add a new strength meloxicam 20 mg/ml. The data for this application were submitted in accordance with Article 13(1) of Directive 2001/82/EC (generic application). The reference product is Metacam 20 mg/ml solution for injection for cattle, pigs and horses. The product was developed in such a way as to closely resemble the chosen reference product and can be considered bioequivalent.

The approved indication is:

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

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

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

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

Benefit assessment

Direct therapeutic benefit

The active substance, meloxicam, is a well-known non-steroidal anti-inflammatory drug in veterinary medicine. The primary mode of action of meloxicam is inhibition of cyclooxygenases in the arachidonic acid inflammatory pathway.

Sufficient justification has been provided to demonstrate that Melovem 20 mg/ml solution for injection is beneficial in reducing clinical signs associated with respiratory disease in cattle, diarrhoea in calves and young non-lactating cattle and acute mastitis in cattle; non-infectious locomotor disorders in pigs and puerperal septicaemia and toxaemia in sows; and acute and chronic musculoskeletal disorders in horses. Consequently it may be considered to benefit animal welfare and aid in the control of inflammatory symptoms associated with the disorders specified in section 4.2 of the SPC. It is expected that the product will have an acceptable safety profile in the target species when administered at the recommended treatment dose.

Additional benefits

Indirect benefits may be considered to arise from the reduction in severity of illness in the agreed indications.

Risk assessment

The formulation and the manufacture of Melovem 20 mg/ml are well described and specifications set will ensure that a product of consistent quality will be produced.

Sufficient justification has been provided to demonstrate that the product will represent the same risks to target animals, users, consumers and the environment as those for the reference product when used as recommended.

It is accepted that the withdrawal periods are the same as those established for the reference product (meat and offal: cattle 15 days, pigs and horses 5 days, milk (cattle) 5 days). The product is not authorised for use in horses producing milk for human consumption.

The same appropriate information and warnings as for the reference product are included in the SPC and product information to minimise risks for the animals, the user, and for the environment.

Risk management or mitigation measures

Appropriate warnings have been included in the SPC to inform on the potential risks to the target animals and the user and the environment and to provide advice for reducing these risks.

Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall. Melovem 20 mg/ml is expected to have the same efficacy as the reference products for the indications as stated in the SPC.

The formulation and manufacture of Melovem 20 mg/ml is well-described and the specifications set will ensure that a product of consistent quality will be produced.

The tolerance and safety profiles are expected to be the same as for the respective reference product; it is well tolerated by the target animals and presents a low risk for users and the environment and appropriate warnings has been included in the SPC. A sufficient withdrawal period has been set.

Conclusion

The overall benefit-risk evaluation is deemed positive with a sufficiently clear and complete SPC and product literature.

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of Melovem 20 mg/ml solution for injection for cattle, pigs and horses are considered to be in accordance with the requirements of Directive 2001/82/EC.