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Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Melovem (EMEA/V/C/000152/X/004)

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 7 July 2009.

This extension application is to add a new strength meloxicam 30 mg/ml solution for injection for cattle and pigs. The reference product is Metacam 20 mg/ml solution for injection for cattle, pigs and horses.

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

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.

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

Melovem 30 mg/ml solution for injection for cattle and pigs 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 30mg/ml solution for injection 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 manufacturing sites are considered in line with legal requirements.

Part 2 - Quality

Composition

Melovem 30 mg/ml solution for injection has been formulated to be essentially similar to Metacam 20 mg/ml solution for injection. Melovem 30 mg/ml solution contains the same active substance (meloxicam) at a higher concentration than the reference product. The formulation includes the following excipients which are partly different from those of the reference product: benzyl alcohol (instead of ethanol), hydrochloric acid, sodium hydroxide, macrogol 1500 (instead of macrogol 300), meglumine, N-methylpyrrolidone (not in the reference product) and water for injections. The following excipients are present in the reference product but not in the proposed formulation: glycine, disodium edetate and Poloxamer 188.

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 Metacam 20 mg/ml solution for injection. The concentration of active in the reference product is publically available and the need to include an antimicrobial preservative in the generic product is based on preservative efficacy data. The applicant has demonstrated that the chosen concentration of benzyl alcohol provides adequate preservation of the formulation but it was not demonstrated that this is the minimum level of preservative that will do so. This aspect of the development of the formulation has not been conducted in accordance with CPMP/CVMP/QWP/115/95. Nonetheless, it is agreed and considered acceptable that levels of benzyl alcohol up to the chosen concentration are commonly used in parenteral products as preservatives. Based on the experience gained during the development of a comparable product and publically available references it was concluded that production of an aqueous solution of meloxicam in a concentration of 30 mg/ml should be possible. Several different solubilisers were tested to increase the aqueous solubility of meloxicam before the final formulation was selected based on solubility and stability considerations.

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 demonstrate 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 certificate of suitability for meloxicam includes 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 (benzyl alcohol, hydrochloric acid, sodium hydroxide, macrogol 1500, meglumine, N-methylpyrrolidone) 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 will 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 are 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 not photo labile.

A freeze/thaw study showed that the product is not sensitive to freezing.

An-use stability was conducted in support of the shelf life after first opening of 28 days. Preservative efficacy was conducted in accordance with Ph. Eur. monograph 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. 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.

Shelf-life 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.

No special storage precautions are required.

Part 3 – Safety

The data for this application are provided in accordance with Article 13(1) of Directive 2001/82/EC (generic application). The chosen reference product is Metacam 20 mg/ml solution for injection for cattle, pigs and horses. No 30 mg/ml strength is authorised for Metacam. For this extension application to include a new strength meloxicam 30 mg/ml the intended target species are cattle and pigs only.

In support of this application, the applicant has provided in vivo bioequivalence studies with the reference product in cattle and pigs (as described in part 4 of this report). Melovem 30 mg/ml was shown to be bioequivalent with the reference product in cattle and pigs.

Additionally, two confirmatory injection site residue depletion studies in cattle and pigs were provided, as required for administration by the intramuscular and subcutaneous routes.

Furthermore, two target animal tolerance studies in cattle and pigs were provided for the evaluation of the local tolerance at the administration site (as described in part 4 of this report).

Safety documentation

Pharmacology

No data in respect of pharmacology are provided. Given that bioequivalence of Melovem 30 mg/ml with Metacam 20 mg/ml is demonstrated (see part 4 of this report), this is considered acceptable.

Toxicological studies

No toxicological studies are provided. Given that bioequivalence of Melovem 30 mg/ml with Metacam 20 mg/ml is demonstrated, as described in part 4 of this report, it is considered that the toxicological profile of the proposed formulation is known and therefore no new data need to be provided.

Local tolerance studies have been provided following administration of the product to cattle and pigs, as described in part 4.

User safety

A user safety assessment was performed in line with the guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/2003-Rev.1) as Melovem 30 mg/ml solution for injection differs from the reference product in terms of composition of both active substance and excipients.

While the user safety assessment provided by the applicant is limited (very brief, limited characterisation of the risk, limited consideration of extent of exposure), the CVMP accepts the overall conclusions on the basis that:

- The principle risk to the user will be from the active substance. While the concentration of meloxicam in Melovem 30 mg/ml is greater that the concentration of meloxicam in the reference product (20 mg/ml), a potential 50% increase in 'worst-case' exposure is not expected to result in an unacceptable risk for the user.
- This application for a marketing authorisation is a line extension to the already existing product Melovem 5 mg/ml solution for injection for cattle and pigs (EU/2/09/098/001), containing largely similar excipients. It can be accepted that the excipients do not pose an unacceptable risk for the user.

Based on the known safety profile of the active substance and excipients from related authorised products, the CVMP accepts that Melovem 30 mg/ml solution for injection does not pose an unacceptable risk to the user and that the user safety statements accepted for the reference product can be applied to Melovem 30 mg/ml solution for injection.

Environmental risk assessment

A Phase I environmental risk assessment was provided in line with the Guideline on Environmental Impact Assessment for Veterinary Medicinal Products – Phase I (CVMP/VICH/592/98-FINAL). Given that the product is used to treat an individual or a few animals in a flock or herd, the environmental risk assessment can stop at Phase I. It is expected that the product will not pose a risk to the environment when used according to the SPC.

Residues documentation

Identification of the product concerned

The formulation used in the residue depletion studies was the final formulation, Melovem 30 mg/ml solution for injection.

Pharmacokinetics

See part 4.

Depletion of residues

The applicant provided two injection site residue depletion studies, conducted in pigs and cattle, as described below.

Given that bioequivalence of Melovem 30 mg/ml with the reference product was established, it can be assumed that residue depletion from principal tissues (muscle, liver, kidney and milk) will occur at a similar rate for both test and reference products.

Given that Melovem 30 mg/ml is to be administered intramuscularly in pigs and subcutaneously in cattle, it is required for generics that, in addition to bioequivalence studies, equivalent (or faster) depletion of residue from the injection site should be demonstrated, according to the Note for guidance – Approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95-FINAL).

Residue depletion study in pigs

The GLP compliant injection site residue depletion study was conducted in accordance with CVMP guideline on injection site residues (EMEA/CVMP/542/03-Final) and the note for guidance - Approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95-Final). Melovem 30 mg/ml was administered to pigs at doses of 0.4 mg of meloxicam/kg bw (equal to 2 ml per 150 kg bw) by intramuscular injection in the neck on two occasions with a between-treatment interval of 24 hours. The animals used in the study had mean weights of 110 kg for males and 250 kg for females and the actual volume administered was in the range of 1.4 – 3.6 ml per animal as a single injection.

Animals were slaughtered in groups of 4 on day 5, day 7 and day 9 after the administration of the product. Core injection site and surrounding tissue samples were harvested and homogenised. Tissue samples were stored frozen pending analysis. Quality control samples and calibration samples were prepared, stored with the test samples and, subsequently, were run in conjunction with test samples.

Meloxicam residues were determined to be below the MRL for muscle (20 µg/kg) in all injection site samples five days after administration of the product. While it is noted that no animals were slaughtered before the proposed withdrawal period of 5 days, the study design was considered sufficient to confirm that by 5 days after administration residues at the injection site were below the MRL.

The analytical methods for determination of meloxicam were satisfactorily validated. Further, quality control samples analysed in conjunction with test samples confirm satisfactory performance of the method.

Residue depletion study in cattle

This GLP compliant injection site residue depletion study was conducted in accordance CVMP guideline on injection site residues (EMEA/CVMP/542/03-Final) and the Note for guidance - Approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95-Final). Melovem 30 mg/ml was administered to cattle at a dose of 0.5 mg of meloxicam/kg bw (equal to 5 ml per 300 kg bw) by subcutaneous injection in the neck on a single occasion. Volumes of test product ranging from 7.0 to 9.5 ml were administered to the test animals at a single site (test animals weighed ~500 kg).

Animals were slaughtered in groups of 4 on day 15 and day 18 after administration of the product. Core injection site and surrounding tissue samples were harvested and homogenised.

Tissue concentrations of meloxicam were below the limit of quantification (10 µg/kg) in samples from all animals at each of the sampling times of 15 days and 18 days post treatment. Meloxicam residues were determined to be below the MRL for muscle (20 µg/kg) in all injection site samples fifteen days after administration of the test item. The study design was considered sufficient to confirm that by 15 days after administration residues at the injection site were below the MRL. Tissue sampling was in line with the CVMP guideline on injection site residues (EMEA/CVMP/542/03). Based on these data, the applicant has satisfactorily demonstrated that the proposed withdrawal period of 15 days (the same as that authorised for the reference product Metacam 20 mg/ml solution for injection) can be retained for Melovem 30 mg/ml when administered by the subcutaneous route to cattle.

The analytical methods for determination of meloxicam were satisfactorily validated. Further, quality control samples analysed in conjunction with test samples confirm satisfactory performance of the method.

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 proposed withdrawal period is:

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

Pigs: Meat and offal: 5 days.

Given that bioequivalence of Melovem 30 mg/ml with the reference product is established and based on the results of the injection site residue depletion studies provided, it is accepted that the withdrawal periods for cattle and pigs as authorised for the reference product can be retained for Melovem 30 mg/ml.

Overall conclusions on the residues documentation

The proposed withdrawal periods of

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

are accepted.

Part 4 – Efficacy

The data for this application are provided in accordance with Article 13(1) of Directive 2001/82/EC (generic application). This extension application is to include a new strength meloxicam 30 mg/ml for the existing target species cattle and pigs. The chosen reference product is Metacam 20 mg/ml solution for injection for cattle, pigs and horses. No 30 mg/ml strength is authorised for Metacam.

In support of this application, the applicant has provided in vivo studies to show bioequivalence of Melovem 30 mg/ml with the reference product in cattle and pigs. The chosen reference product for both bioequivalence studies is Novem 20 mg/ml solution for injection, a centrally authorised product

which is similar to Metacam 20 mg/ml solution for injection by the same MAH as Metacam. CVMP considers the choice of the reference product as justified.

Additionally, local tolerance studies in cattle and pigs were provided.

Pharmacodynamics

No data provided.

Development of resistance

Not applicable.

Pharmacokinetics

Bioequivalence study in pigs

A GLP compliant comparative pharmacokinetic study in a two treatment, two-period crossover design with a wash out period of 48 hours was performed to show bioequivalence of Melovem 30 mg/ml with Novem 20 mg/ml solution for injection after a single intramuscular administration to pigs. The chosen wash out period of 48 hours was in excess of ten half-lives for the active meloxicam in pigs and is considered appropriate.

Twenty six, eleven-week old clinically healthy castrated male pigs of a mean weight of 32.6 kg received an intramuscular injection of 0.4 mg meloxicam/kg (equal to 2 ml per 150 kg bodyweight) in the neck. Plasma samples were collected before and after administration of the products. Samples were frozen until analysed for meloxicam content using a validated method. Quality control samples and calibration samples were prepared and run in conjunction with test samples.

The results were used to calculate C_{max}, T_{max}, AUC_{last} and AUC_{tot}. The primary parameters for demonstration of bioequivalence C_{max} and AUC values were analysed by ANOVA after log transformation. Upper and lower limits of the 90% confidence intervals were calculated with the estimated error variance found in the ANOVA tables.

The 90% confidence intervals for AUC and C_{max} fell within the specified limits which, in accordance with the EMEA/CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00) was considered demonstrative of bioequivalence. Based on the findings of the study, CVMP considers that bioequivalence was shown between Melovem 30 mg/ml and the reference product following intramuscular administration to pigs.

Bioequivalence study in cows

A GLP compliant comparative pharmacokinetic study in a two treatment, two-period crossover design with a wash out period of 28 days was performed to demonstrate bioequivalence of Melovem 30 mg/ml and Novem 20 after a single subcutaneous administration in the neck to cows. The chosen wash out period of 28 days was in excess of ten half-lives for the active meloxicam in pigs and is considered appropriate.

Twelve, clinically healthy lactating dairy cows, weighing 540.0 ± 34.3 kg received a subcutaneous injection of 0.5 mg meloxicam/kg (equal to 5 ml per 300 kg bodyweight) in the neck. Plasma samples were collected before and at various time intervals after administration of the products and were analysed for meloxicam content using a validated method. Quality control samples and calibration samples were prepared and run in conjunction with test samples.

The results were used to calculate C_{max}, T_{max}, AUC_{last} and $T_{1/2}$. C_{max} and AUC values were analysed by ANOVA after log transformation. Upper and lower limits of the 90% confidence intervals were calculated with the estimated error variance found in the ANOVA tables.

For demonstration of bioequivalence, the primary parameters were considered to be AUC_{last} and C_{max}. The 90% confidence intervals for AUC and C_{max} fell within the specified limits, which, in accordance with the EMEA/CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-rev.2), can be considered demonstrative of bioequivalence. Based on the findings of the study, CVMP considers that bioequivalence was shown between Melovem 30 mg/ml and the reference product following subcutaneous administration to cattle.

Dose determination/justification

Not applicable.

Target animal tolerance

Where bioequivalence with an authorised reference product has been demonstrated, it is generally accepted that data on the systemic tolerance of the product in the target species is not required. However, for injectable products, data to confirm acceptable local tolerance in target species should be provided. The applicant provided the results of local tolerance studies in cattle and pigs following the administration of the product to those species.

Local tolerance study in pigs

A GLP compliant study was performed in accordance with the guideline on target animal safety for pharmaceuticals (EMEA/CVMP/VICH/393388/2006) to evaluate local tolerance to Melovem 30 mg/ml following intramuscular injection in clinically healthy pigs of the Piétrain breed, aged 13 months and with body weights of 41.1 – 55.6 kg. Melovem 30 mg/ml was administered intramuscularly in the neck to eight animals (four castrated males and four female) at a dose of 0.4 mg meloxicam /kg bodyweight on two occasions with a between treatment interval of 24 hours. The animals in the control group (four castrated males and four female) were administered saline at doses of 2 ml per 150 kg bw. Immediately before administration, 1, 2, 4, 6, 24 and 30 hours after each administration, injection sites were examined by inspection, palpation and were assessed for appearance (size), inflammation (painfulness and warmth), oedema or other changes. Blood samples were collected for the determination of creatinine phosphokinase (CPK) and aspartate transaminase (AST) before and approximately 1, 3, 6 and 24 hours after each administration of the test and control products. Injection sites were examined grossly and histopathologically.

On the basis of the injection site scores, it is evident that a slight swelling may result at the site of injection following intramuscular administration to pigs. However, it would appear that the swelling is transient and was recorded as having disappeared by 2 hours post injection. The pathological changes observed would appear to be expected and acceptable changes following intramuscular administration. Given the very transient nature of the swelling and the nature and severity (mild) of the pathological change, it is accepted by CVMP that the product is well tolerated locally, at the injection site, following intramuscular administration to pigs.

Local tolerance study in cattle

A GLP compliant study was performed in accordance with the guideline on target animal safety for pharmaceuticals (EMEA/CVMP/VICH/393388/200) to evaluate local tolerance to Melovem 30 mg/ml following subcutaneous injection in clinically healthy dairy cows with body weights of 402 – 635 kg. Melovem 30 mg/ml was administered once on day 1 intramuscularly in the neck to eight animals at

doses of 0.5 mg meloxicam/kg bodyweight (equal to 5 ml of Melovem 30 mg/ml). The animals in the control group were administered saline at doses of 5 ml per 150 kg bw. Immediately before administration, 1, 3, 6, 24, 30, 48 and 72 hours after administration, injection sites were examined by inspection, palpation and were assessed for appearance (size), inflammation (painfulness and warmth), oedema or other changes. Blood samples were collected for the determination of creatinine phosphokinase (CPK) and aspartate transaminase (AST) before and approximately 1, 3, 6, 24, 27, 30, 48 and 72 hours after administration of the test and control products. Injection sites were examined grossly and histopathologically.

Based on the injection site scores, it is evident in cattle that transient, non-painful swelling may result at the site of injection in some animals. The SPC of the reference product Metacam 20 mg/ml solution for injection contains information relating to the potential for transient injection site reactions following subcutaneous administration to cattle.

Given the findings of the above study, it is accepted by CVMP that the product is well tolerated, but considers it appropriate to include the same text in the SPC for Melovem 30 mg/ml solution for injection as appears in sections 4.6 and 4.10 of the SPC for the reference product.

Field trials

No data were provided. Given the type of application (a generic) and the fact that Melovem 30 mg/ml solution for injection is considered bioequivalent with the reference product, the omission of field studies is acceptable.

Overall conclusion on efficacy

In support of this application in vivo bioequivalence studies were provided which show that Melovem 30 mg/ml solution for injection can be considered bioequivalent to the reference product Metacam 20 mg/ml solution for injection when administered subcutaneously in cattle and intramuscularly in pigs. Therefore, it can be concluded that Melovem 30 mg/ml will be as efficacious as the reference product and that systemic tolerance can be considered to be the same as for the reference product.

Local tolerance studies confirm acceptable tolerance of the product at the injection site in both cattle when administered subcutaneously and in pigs when administered intramuscularly. However, as transient swelling is a feature of Melovem 30 mg/ml when administered subcutaneously in cattle, the potential for this effect is reflected in the SPC with the same text as in the SPC of the reference product.

Part 5 – Benefit-risk assessment

Introduction

Melovem 30 mg/ml solution for injection for cattle and pigs is an extension application to add a new strength meloxicam 30 mg/ml for the existing target species cattle and pigs. The data is submitted in accordance with Article 13(1) of Directive 2001/82/EC (generic application). The chosen reference product is Metacam 20 mg/ml solution for injection for cattle, pigs and horses. No 30 mg/ml strength is authorised for Metacam. The target species for Melovem 30 mg/ml are cattle and pigs only.

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.

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.

Evidence has been provided to demonstrate that Melovem 30 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. 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 above conditions.

Risk assessment

The formulation and the manufacture of Melovem 30 mg/ml are well described and specifications set will ensure that a product of consistent quality will be produced.

Evidence 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. Well-controlled studies confirm acceptable local tolerance in target species.

It is accepted that the withdrawal periods are the same as those established for the reference product (meat and offal: cattle 15 days, pigs 5 days, milk (cattle) 5 days).

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 30 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 30 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 have been included in the SPC. An adequate 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 30 mg/ml solution for injection for cattle and pigs are considered to be in accordance with the requirements of Directive 2001/82/EC.