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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Meloxidolor (EMEA/V/C/002590)

International non-proprietary name: Meloxicam

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

Introduction

An application for the granting of a community marketing authorisation was submitted to the European Medicines Agency (The Agency) on 1 December 2011 by Le Vet Beheer B.V. for Meloxidolor 5 mg/ml solution for injection for dogs, cats, cattle and pigs, 20 mg/ml solution for injection for cattle, pigs and horses and 40 mg/ml solution for injection for cattle, pigs and horses, through the centralised procedure in accordance with Article 3(3) of Regulation (EC) No. 726/2004.

The eligibility for the centralised procedure was agreed upon by the CVMP on 7-9 July 2011.

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

The legal basis for this application is Article 3(3) of Regulation (EC) 726/2004 and the application is submitted in accordance with Article 13(3) of Directive 2001/82/EC. This hybrid application is based on the reference medicinal products Metacam 5 mg/ml solution for injection for dogs and cats, Metacam 5 mg/ml solution for injection for cattle and pigs and Metacam 20 mg/ml solution for injection for cattle, pigs and horses.

Meloxidolor solution for injection contains meloxicam (a NSAID) as active ingredient at concentrations of 5 mg/ml, 20 mg/ml and 40 mg/ml. Meloxidolor 5 mg/ml is presented in glass vials of 10 ml, 20 ml and 100 ml. Meloxidolor 20 mg/ml and 40 mg/ml solution are presented in glass vials of 50 ml and 100 ml.

The route of administration is intramuscular, intravenous or subcutaneous. The target species are dogs, cats, cattle, horses and pigs.

The proposed target species, indications and routes of administration for the 5 mg/ml strength are detailed below and are identical to those included in the SPCs of the reference products, Metacam 5 mg/ml solution for injection for dogs and cats and Metacam 5 mg/ml solution for injection for cattle and pigs. The proposed target species, indications and routes of administration for the 20 mg/ml strength are identical to those for Metacam 20 mg/ml solution for injection for cattle, pigs and horses as listed below. The proposed target species, indications and routes of administration for the 40 mg/ml strength are the same as Metacam 20 mg/ml solution for injection for cattle, pigs and horses as there is not a respective strength authorised for Metacam.

Meloxidolor 5 mg/ml:
Dogs (intravenous or subcutaneous use): Alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders and the reduction of post-operative pain and inflammation following orthopaedic and soft tissue surgery.

Cats (subcutaneous use)**:** Reduction of post-operative pain after ovariohysterectomy and minor soft tissue surgery.

Cattle (intravenous or subcutaneous use)**:** 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.;

Pigs (intramuscular use)**:** For use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation; for the relief of post-operative pain associated with minor soft tissue surgery such as castration.

Meloxidolor 20 mg/ml and 40 mg/ml:
Cattle (intravenous or subcutaneous use)**:** 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 (intramuscular use)**:** 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 (intravenous use)**:** For use in the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders; or the relief of pain associated with equine colic.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on bibliographic literature and with appropriate non-clinical data produced by the applicant. Justification for waiving bioequivalence studies is provided.

The CVMP adopted an opinion and CVMP assessment report on 7 February 2013.

On 22 April 2013, the European Commission adopted a Commission Decision for this application.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant provided a detailed description of the pharmacovigilance system. Based on this documentation it is considered that a pharmacovigilance system is in place that 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

The manufacturing site is appropriately authorised for manufacture of the product in accordance with EU Good Manufacturing Practice (GMP), a GMP certificate was provided.

For the active substance an active substance master file (ASMF) was provided. The manufacturing authorisation and the GMP status are adequately documented and acceptable.

No inspections are requested.

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

The proposed veterinary medicinal product is an aqueous solution for injection containing meloxicam at three different concentrations of 5, 20 and 40 mg/ml.

The excipients used in the formulations (Poloxamer 188, glycofurol, glycine, meglumine, sodium chloride, sodium hydroxide and hydrochloric acid) are all well-known and are established in other medicinal products, including other solutions for injection. The proposed compositions include ethanol

as antimicrobial preservative and several solubilising agents are included as the active substance is practically insoluble in water.

The proposed compositions of the Meloxidolor 5 mg/ml and 20 mg/ml presentations are claimed to be qualitatively and quantitatively identical (both in active substance and excipients) to those of the reference medicinal products. As for the 40 mg/ml presentation, the reference medicinal product does not have such strength authorised. The proposed composition of the 40 mg/ml strength is qualitatively identical to the 20 mg/ml solution of the reference product and differs quantitatively only in the concentrations of the active substance and of the solubilising agent meglumine.

Container

The product is presented in colourless type I glass vials, closed with bromobutyl stopper and aluminium caps in the proposes pack sizes are 10 ml, 20 ml, 50 ml and 100 ml.

Development pharmaceutics

The aim of the development pharmaceutics for the 5 and 20 mg/ml strengths was to develop such solutions for injection which are qualitatively and quantitatively identical in both the active substance and in the excipients to the reference medicinal products Metacam 5 mg/ml solution for injection and Metacam 20 mg/ml solution for injection.

The key point for the assessment of the development pharmaceutics is the relationship between the type of application (a so called 'hybrid') and the requirements for waivers from bioequivalence study requirements for solutions for injection. For the 5 mg/ml and 20 mg/ml solutions the exemption of bioequivalence studies was granted because for the intravenous (IV) administration they fulfil the conditions as stated in paragraph 7.1.a), and for subcutaneous (SC) or intramuscular (IM) administration they fulfil the conditions stated in paragraph 7.1.b) of the guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2).

Regarding the 40 mg/ml solution, the proposed composition has been satisfactorily justified and differences in the quality profile in respect to the 20 mg/ml are not expected. After intravenous injection the solution is immediately diluted in the blood and the volume to be injected is only 50% of the volume that needs to be injected for the 20 mg/ml strength as the posology is the same.

Other points of the development pharmaceutics are acceptable.

Method of manufacture

Detailed descriptions of the method of manufacture have been provided.

The manufacturing process is a standard one and consists of the preparation of the bulk solutions by successive dissolution of the components into the water for injection, the filtration of the final bulk solution through a sterilising filter under aseptic conditions and the filling of the filtered solution into the vials. Finally, the filled and closed vials are sterilised by autoclaving. The addition of the different components has to be done in a particular order and the temperature of the water for injections at the beginning of the process and of the successive intermediate solutions is controlled to stay within pre-set ranges.

The validation of the manufacturing process will be performed on the first three consecutive production batches according to the provided proposed validation protocols.

Control of starting materials

Active substance

For the active substance, meloxicam, an active substance master file (ASMF) was provided which had been assessed before for previous applications of the applicant.

All additional assays and specifications from the manufacturer of the active substance are also included in the specifications and routine assays adopted by the applicant which is considered acceptable.

The stability studies of the active substance support the proposed retest period of 2 years when stored in double polyethylene bags inside of fibre drums.

Excipients

All of the excipients, except glycofurol, are controlled in accordance with their European Pharmacopoeia (Ph. Eur.) monographs. For the quality control of glycofurol an acceptable internal monograph of the manufacturer is available.

All excipients used in the formulation of Meloxidolor are commonly used in human and veterinary medicinal products and have a well-known toxicological profile. The excipients are justified and acceptable.

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

None of the starting materials used for the production of the finished product fall within the scope of the guidance "Note for guidance on minimising the risk of Transmitting animal Spongiform Encephalopathy agents via Human and Veterinary Medicinal Products" (EMEA/410/01 rev.3).

Control tests during production

Not applicable.

Control tests on the finished product

A clear declaration of the proposed release specifications for the finished products is available and complies with the minimum requirements of the Ph. Eur for the dosage form and with the general principles of the guidelines VICH GL39 and Note for Guidance 3AQ11a: Specifications and Control Tests on the Finished Product. Control tests of the finished products are deemed satisfactory taking into the account the composition and the manufacturing process of the medicinal product.

The established shelf life specifications are the same as for release.

Stability

Results of stability tests with the active substance are available on batches under accelerated conditions (6 months) at 40 °C/75% RH and long-term conditions (up to 60 months) at 25 ºC and 60% RH. The proposed retest period for the active substance is 2 years, stored in double polyethylene bags in fibre drums. No relevant changes were observed. The results support the claimed re-test period of two years and is therefore acceptable.

Results of stability studies with the finished product are available for 6 months under accelerated conditions at 40 °C/75% RH and 12 months from an on-going study under long term conditions at

25 ºC and 60% RH (planned for 36 months). Based on the currently available stability data for Meloxidolor 5 mg/ml, 20 mg/ml and 40 mg/ml strength, a shelf-life of 24 months can be granted.

The long-term stability studies will continue for a maximum period of 3 years after manufacturing.

In-use stability data are available on batches stored under uncontrolled conditions (climatic zone 1) for 9 months and stored under long term conditions (25 °C/60% RH) at 36 months. Based on these results, an in-use shelf-life after first opening of the container of 4 weeks is considered acceptable.

All stability tests were performed in compliance with the respective VICH standards.

No photostability study was provided. According to the guideline EMEA/CVMP/QWP/846/99-Rev.1 on stability testing of existing active substances and related finished products, photostability testing should be conducted on at least one primary batch of the finished product. However, taking into the account that the reference medicinal product is packed in clear vials (as well as all the solutions for injection authorised as generics of it) it is acceptable to omit the photostability study of the finished product.

Overall conclusions on quality

The data provided in part 2 of the dossier are in line with VICH and Ph. Eur. requirements and are acceptable. The internal monograph by the final manufacturer for glycofurol is considered acceptable. The product is a solution for injection which utilises standard pharmaceutical excipients. The proposed formulation for the 40 mg/ml strength (a respective strength of the reference medicinal product is not available) has been satisfactorily justified and it has been shown that significant differences in the quality profile respect to the reference 20 mg/ml solution are not expected. The method of manufacture is a standard process and the specifications of the finished product are satisfactory for the proposed composition and dosage form. The active substance is monographed in the Ph. Eur. The active substance and the formulated products are considered to be stable.

Part 3 – Safety

This application has been made in accordance with Article 13(3) of Directive 2001/82/EC (a hybrid application). The reference products cited by the applicant that have been authorised within the EU are Metacam 5 mg/ml solution for injection in dogs and cats, Metacam 5 mg/ml solution for injection for cattle and pigs and Metacam 20 mg/ml solution for injection for cattle, pigs and horses.

According to the current bioequivalence guideline (EMEA/CVMP/016/00-Rev.2) the exemption of bioequivalence studies can be granted for the 5 and 20 mg/ml strength; for the intravenous administration they fulfil the conditions stated in paragraph 7.1.a), and for subcutaneous or intramuscular administration they fulfil the conditions stated in paragraph 7.1.b).

Regarding the 40 mg/ml strength, the chosen reference product is Metacam 20 mg/ml. No 40 mg/ml strength is authorised for Metacam. However, as the active substance concentration is different, the applicant considers it as hybrid instead of a generic. The applicant has submitted a satisfactory dossier including peer-reviewed literature to justify the safety of this for this strength. A detailed and critical summary on the safety documentation is largely based on published scientific literature. Nevertheless, the bioequivalence guideline does not give an exemption from the need to conduct in vivo bioequivalence studies where the test product differs in concentration of the active substance/excipients from the reference product and is administered subcutaneously or intramuscular. Hence, appropriate in vivo bioequivalence studies with Meloxidolor 40 mg/ml are deemed necessary for SC administration in cattle and IM administration in pigs. As no studies were provided it cannot be concluded whether the 40 mg/ml strength will have the same safety profile as the reference product

when administered subcutaneously in cattle and intramuscularly in pigs. As a consequence for Meloxidolor 40 mg/ml the application for a subcutaneous route of administration in cattle and the target species pigs were withdrawn by the applicant during the procedure.

All excipients used in the formulation of Meloxidolor are commonly used in human and veterinary medicinal products and have a well-known toxicological profile. Therefore, it is expected that they will not raise a toxicological concern for the safety of the user, the target animals and for the environment.

Safety documentation

Pharmacodynamics

See part 4 of this report.

Pharmacokinetics

See part 4 of this report.

Toxicological studies

Single dose toxicity:

The oral LD50 value was 83.5 mg/kg in the most sensitive species/strain tested (Chbb:THOM rats). Decreased motor activity, black faeces and anaemia were observed. At necropsy of dead rats, perforated gastric and intestinal ulcers as well as peritonitis with haemorrhagic ascites were found.

Repeated dose toxicity:

Chronic toxicity studies carried out in rodents and dogs showed clinical and clinico-pathologic signs of the gastrointestinal tract and the kidney. These were shown to be the toxicological target organs. In a 3-month study, rats were dosed orally by gavage with 1.0, 3.5 or 10.0 mg/kg bw; the No Observed Effect Level (NOEL) was 1.0 mg/kg bw in this study. In the 6-month study the determination of a NOEL was not possible because some minor or significant effects were observed in the lowest dose groups. Based on the results of a one-year GLP compliant chronic oral dog study, the NOEL was considered to be 0.8 mg/kg bw.

Tolerance in the target species of animal:

Tolerance studies are addressed in part 4 of this report. The most common adverse effect attributed to the use of any NSAID is gastrointestinal (GI) distress manifested by gastric pain, vomiting and diarrhoea because of GI erosions, ulceration and haemorrhage. Hepatic, renal, central nervous system, dermatological and hematologic systems are also systems that can be adversely affected.

Reproductive toxicity:

The No Observed Adverse Effect Level (NOAEL) in foetuses was considered to be 8 mg/kg. The dose of 20 mg/kg was considered to be the threshold for embryo lethal effects. Meloxicam was not teratogenic in rabbits.

The results of a study in rats indicate that the maternal NOAEL is 0.125 mg/kg bw/day. For the reproductive and developmental parameters, it is less than 0.125 mg/kg bw/day for dams and offspring.

Mutagenicity/genotoxicity: No evidence of potential genotoxicity related to meloxicam was found.

Carcinogenicity: No carcinogenic effect of meloxicam was observed in rats or in mice.

Studies of other effects

The potential of immunogenic effects of meloxicam has been investigated. No evidence of any immunogenic effects of meloxicam was seen in any of these tests.

No evidence of potential phototoxicity related to meloxicam was found.

The studies show that meloxicam does not have degenerative effects on cartilage.

User safety

No bioequivalence studies were provided which is acceptable according to the current bioequivalence guideline (EMEA/CVMP/016/00-Rev.2) for the 5 and 20 mg/ml strengths. However, as Meloxidolor 5 mg/ml and 20 mg/ml can be considered bioequivalent with the reference products Metacam 5 mg/ml and Metacam 20 mg/ml it can be assumed that for Meloxidolor 5 mg/ml and 20 mg/ml the same risks for the user as for the reference products will apply.

A user risk assessment for Meloxidolor 40 mg/ml has been performed according to the current guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1) with focus on the potential extra risk caused by the increased concentrations of meloxicam and meglumine. Meloxidolor 40 mg/ml is considered to have the same risks for the user as the reference product Metacam 20 mg/ml solution for injection.

The same warnings as for the reference products are included in section 4.5 of the SPC.

Additionally, as meloxicam showed to be embryotoxic/reprotoxic the following sentence "*Meloxicam may be harmful for the foetus and unborn child. Pregnant women and women of child-bearing potential should not administer this product*" has been added to section 4.5 of the SPC for all three strengths.

In conclusion, taking into account the addition above concerning embryotoxicity and reproduction toxicity, the proposed risk management sentences in the SPC are considered appropriate to ensure user safety.

Environmental risk assessment

The veterinary medicinal product will be used in both food producing and non-food producing animals. In both cases it will be used to treat individual or a small number of animals in a flock or herd.

According to the Guideline on environmental impact assessment (EIAs) 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 as recommended.

Overall conclusions on the safety documentation

A detailed and critical summary on the safety documentation is largely based on published scientific literature. The applicant has submitted a satisfactory dossier including peer-reviewed literature. Meloxicam is a well-known substance and has been used in veterinary medicines for many years and therefore this approach is considered acceptable. As Meloxidolor 5 mg/ml and 20 mg/ml are considered bioequivalent with the respective authorised reference products it can be assumed that Meloxidolor will pose the same risk to the target animals, the user and the environment as the reference products and the same safety warnings are included in the SPC.

Nevertheless, the bioequivalence guideline does not give an exemption from the need to conduct in vivo studies where the test product differs in concentration of the active substance/excipients from the

reference product and is administered by the SC or IM routes. This applies to the initially claimed use of the 40 mg/ml strength subcutaneously in cattle and intramuscularly in pigs. As such studies were not provided consequently the subcutaneous use in cattle is no longer proposed and the target species pigs were withdrawn for this strength. The provided assessment of the user safety for the 40 mg/ml strength allows the conclusion that Meloxidolor 40 mg/ml will have the same risks to the user as the reference product and the same safety warnings apply. Meloxidolor 40 mg/ml is expected not to pose a risk to the environment when used according to the label instructions.

Residues documentation

Residue studies

No new studies have been provided.

Pharmacokinetics

No studies on pharmacokinetics were performed with Meloxidolor. See part 4.

Depletion of residues

No residue depletion studies were provided for Meloxidolor 5 mg/ml and 20 mg/ml as they are considered to be bioequivalent with the reference products (Metacam 5 mg/ml and Metacam 20 mg/ml) and satisfactory justification for the retention of the same withdrawal periods was provided.

A residue depletion and local tolerance study was carried out with Meloxidolor 40 mg/ml to determine the withdrawal period in pigs after intramuscular administration of 0.4 mg meloxicam/kg bw. The study was designed as a one site, non-blinded, randomised, residue depletion study. Meloxidolor 40 mg/ml solution for injection was intramuscularly administered to 16 healthy animals at a dose of 0.4 mg meloxicam/kg bw in the post auricular area on the first day and on the second day, 24 hours apart, into different sides of the neck. Target tissues (muscle including injection site, liver and kidney), histological samples of the injections site (IS) and blood chemistry (aspartate aminotransferase AST and creatine phosphokinase CPK) samples were collected. Kidney, liver and muscle samples including injection site were collected 4 hours, 1, 3 and 5 days after the second (last) administration. A lower mass of samples than generally recommended (47% and 55% of recommended amount) was collected from the injection site and surrounding area but it is accepted with respect to physiological proportion of experimental animals. The analytical method used was a validated LC-MS/MS method.

Meloxicam was rapidly eliminated from examined tissues. Residues above the MRLs were detected in all examined tissues only at 4 hours after the last treatment. At one day after treatment, residues above the MRLs were only detected in kidney (95.5, 102.7 and 121.2 µg/kg) and injection site samples (21.4 and 23.5 µg/kg). Residues at three and five days after treatment were all below the limit of quantification (LOQ).

Based upon the results of the study provided, residue concentrations of Meloxicam above the LOQ for all tissues (kidney 32.5 µg/kg, liver 32.5 µg/kg, muscle 10.0 µg/kg) were not detected in muscle, liver, kidney or fat samples in animals slaughtered three and five days after the final administration of the product.

As the target species pig was withdrawn for the 40 mg/ml strength during the procedure the depletion study in pigs is redundant.

No injection site residue depletion study was provided for subcutaneous use of Meloxidolor 40 mg/ml in cattle which is considered not acceptable. Consequently, the subcutaneous route of administration in cattle was removed for Meloxidolor 40 mg/ml.

MRLs

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

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

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

Withdrawal periods

As Meloxidolor 5 mg/ml and 20 mg/ml are considered bioequivalent with the reference products (see parts 1 and 4), the withdrawal periods (meat and offal and, where applicable, milk (cattle)) for Meloxidolor 5 mg/ml and 20 mg/ml are the same as the established withdrawal periods of the reference products (cattle: meat and offal 15 days, milk 5 days (20 mg/ml), pigs and horses: meat and offal 5 days). Meloxidolor is not authorised for use in horses producing milk for human consumption.

Based upon the results of the residue depletion study conducted with Meloxidolor 40 mg/ml in pigs all meloxicam concentrations were found to be below the LOQ of all tissues from day three onwards following intramuscular administration. A withdrawal period was derived based on alternative approach recommended by the CVMP Note for guidance: Approach towards Harmonisation of Withdrawal Periods (EMEA/CVMP/036/95-FINAL), as the obtained data did not permit statistical model (regression analysis). The results confirmed that a withdrawal period of 5 days (meat and offal) for pigs for a 40 mg/ml strength formulation could be acceptable. However, as pigs are withdrawn as target species for the 40 mg/ml strenth, these findings are considered not relevant for this application.

For intravenous use of Meloxidolor 40 mg/ml in cattle and horses, it is considered appropriate to extrapolate the withdrawal periods from the reference product (20 mg/ml) in accordance with section 7.1(a) of the bioequivalence guideline (EMA/CVMP/016/00-Rev.2) as the product contains the same active ingredient and the posology is the same, with the same dose of meloxicam given when treated with either the 20 mg/ml or the 40 mg/ml formulation.

Overall conclusions on the residues documentation

The established withdrawal periods of the reference products as listed below are applied for Meloxidolor 5 mg/ml (cattle and pigs), 20 mg/l (cattle, pigs and horses) and 40 mg/ml (cattle and horses):

Cattle:

Meat and offal: 15 days

Milk: 5 days (only for Meloxidolor 20 and 40 mg/ml)

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 - Pre-clinical and clinical trials

This application has been made in accordance with Article 13(3) of Directive 2001/82/EC, as amended (a hybrid application). The reference products chosen by the applicant that have been authorised within the EU are Metacam 5 mg/ml solution for injection in dogs and cats, Metacam 5 mg/ml solution for injection in dogs and cats and Metacam 20 mg/ml solution for injection for cattle, pigs and horses.

No in vivo bioequivalence studies were provided. According to current bioequivalence guideline (EMEA/CVMP/016/00-Rev.2) the exemption of in vivo bioequivalence studies can be granted for the 5 and 20 mg/ml strength; for the intravenous administration they fulfil the conditions stated in paragraph 7.1.a), and for subcutaneous or intramuscular administration they fulfil the conditions stated in paragraph 7.1.b).

Regarding the 40 mg/ml solution, the claimed reference medicinal product is Metacam 20 mg/ml and, because the active substance concentration is different, the application is a hybrid one instead of a generic. The applicant has submitted a satisfactory dossier including peer-reviewed literature to justify most aspects of safety of the product. A detailed and critical summary on the preclinical documentation is largely based on published scientific literature. Nevertheless, the bioequivalence guideline does not give an exemption from the need to conduct in vivo studies where the test product differs in concentration of the active substance/excipients from the reference product and is administered by the SC or IM routes which applies to the 40 mg/ml strength subcutaneously in cattle and intramuscular in pigs. As such studies were not provided no conclusions can be drawn whether the 40 mg/ml will have the same efficacy as the reference product when administered SC in cattle and IM in pigs. Consequently the subcutaneous use in cattle was withdrawn and the target species pigs is no longer proposed for this strength.

Pre-clinical studies

Pharmacodynamics

Peer-reviewed published literature was provided by the applicant to document the pharmacodynamic properties of the active substance, meloxicam. As this is a generic application and bioequivalence is

established between Meloxidolor and the reference product, the sections 5.1 and 4.2 of the SPC of Meloxidolor are the identical to those of the reference product.

The mechanism of action of meloxicam is inhibition of the cyclooxygenase (COX) enzyme, with preference to COX-2. Three isoforms of COX are known: COX-1, COX-2 and COX-3. COX-1 has been identified in many healthy organs and cells, such as the stomach, kidney, nervous system and platelets whereas COX-2 is found in higher amounts in inflamed tissues. The revision of the public literature provided by the applicant summarises the principal pharmacodynamic effects of meloxicam on the central nervous system, anticonvulsant effects, spasmolytic activity in vitro, influence on gastrointestinal tract, water and electrolyte excretion, effects on body weight, thymus and adrenal gland weight of the rat after 14 days of administration, effects on heart, circulation and respiration, in vitro and in vivo effects of COX-specific inhibitors and effects on renal function. No different effects than those well known for meloxicam have been found.

Development of resistance

Not applicable.

Pharmacokinetics

No pharmacokinetics studies in the target species have been provided by the applicant. A number of publicly available literature on studies in laboratory animals (rats) were provided. The main conclusions are summarised below:

Absorption:

Different studies in rat have been presented. Based on urinary ^{14}C-meloxicam excretion data, oral absorption was ~95%. Meloxicam is absorbed over a relatively long section of the gastrointestinal tract. Although blood concentrations were virtually identical in male and female rats during the initial distribution phase, a clear gender difference emerged during the longer elimination phase, with females demonstrating considerably higher concentrations, resulting from a slower rate of elimination. Protein binding after oral administration of ^{14}C-meloxicam (0.5 mg/kg) was high in both male and female animals (99.5–99.7%).

Distribution:

The highest tissue concentrations of radioactivity after either oral (5 mg/kg) or IV (1 mg/kg) dosing were found in the liver. The distribution was investigated in male and female rats after multiple oral doses of ^{14}C-meloxicam (1 mg/kg/day for 5 days). Steady-state conditions were achieved by the third dose in both genders. The highest concentrations of radioactivity were detected in blood, liver and kidneys, with low levels in the brain (2-3% of those found in plasma).

Excretion:

Renal excretion was the main route of elimination in rats, accounting for approximately 70% of the orally or IV administered ^{14}C-meloxicam dose (1 mg/kg). Elimination in lactated milk was studied in rats nursing 9-11-day-old pups. Oral administration of ^{14}C-meloxicam (5 mg/kg) resulted in higher concentrations of radioactivity in milk than in plasma at 5 hr (22.3 versus 18.4 mg/l) and 24 hr (9.9 versus 6.0 mg/l) after dosing.

As these data were not derived from target animals they are not considered relevant for the SPC.

Target animal tolerance

No target animal tolerance studies were provided for Meloxidolor 5 mg/ml and 20 mg/ml solution for injection. As both strengths are considered bioequivalent with the respective reference products it can be concluded that the tolerance profile of the 5 mg/ml and 20 mg/ml strength will be the same as for the reference products. Consequently it can be concluded that at the recommended dose these strengths are well tolerated in dogs, cats, cattle and pigs. The expected tolerance profile of the 5 mg/ml and 20 mg/ml strength in the field are the same as for the reference products.

For Meloxidolor 40 mg/ a local tolerance study in pigs, in addition to supportive literature, has been provided. The study design deviated from the target animal safety guideline CVMP/VICH/393388/2006. Results showed that a rapid increase of CPK activity was recorded in most animals after the intramuscular administration which was explained to be caused by stress during the blood sampling. Nevertheless the post mortem examination revealed lesions in injection site in two groups 2 and 4 days after administration which were light scars with no encapsulated tissue. Only one lesion with encapsulated tissue debris less than 1 cm3 was found two days after administration. No visible abnormalities were found in time intervals three, five and six days. Similar observations were found by Stei et al (1996) during a local tolerance study of meloxicam.

In addition a publication by Magyar et al (2007) was provided which described a blind, positively controlled, randomised clinical study with Metacam 20 mg/ml solution for injection after a single intramuscular administration in pigs in comparison to a flunixin containing solution for injection. The results of this study show that meloxicam administered intramuscularly will give significantly less severe macroscopic and histopathological lesions than the comparator flunixin meglumine solution. As in this study meloxicam 20 mg/ml injectable solution was used no conclusions can be drawn for the higher concentration of 40 mg/ml injectable solution.

No specific local tolerance studies have been performed with the 40 mg/ml strength for cattle and horses. As this was considered by CVMP being not acceptable for the subcutaneous use of the 40 mg/ml strength in cattle, the initially claimed subcutaneous administration route in cattle was withdrawn for Meloxidolor 40 mg/ml. Hence, for Meloxidolor 40 mg/ml only the intravenous route of administration is acceptable for cattle and horses; after intravenous injection the solution is immediately diluted in the blood and the volume to be injected is only 50% of the volume that needs to be injected for the meloxicam 20 mg/ml as the posology is the same. Unexpected adverse events with respect to local and systemic tolerance are not to be expected.

Field trials

Field trials are not applicable for this type of application, considering that bioequivalence with the reference products for the 5 mg/ml and 20 mg/ml strength is established. This applies to the 40 mg/ml strength as well as this will be administered intravenously only and the biowaiver is therefore acceptable.

Overall conclusion on efficacy

The applicant has submitted a dossier including peer-reviewed literature and a study on local tolerance in pigs.

A detailed and critical summary on the preclinical documentation is largely based on published scientific literature.

No in vivo bioequivalence studies were provided. According to the current bioequivalence guideline (EMEA/CVMP/016/00-Rev.2) the exemption of bioequivalence studies can be granted for the 5 mg/ml

and 20 mg/ml strength because for the intravenous administration they fulfil the conditions stated in paragraph 7.1.a), and for subcutaneous or intramuscular administration they fulfil the conditions stated in paragraph 7.1.b). As the toxicological profile of all excipients of the product is well known, they are not expected to raise toxicological concerns for the animal safety. Hence no specific tolerance studies, in order to determine margins of safety in the target species, are required.

Given that bioequivalence of Meloxidolor 5 mg/ml and 20 mg/ml with the reference products is established, it is accepted that the efficacy and the clinical tolerance of these strengths will be the same as for the reference products.

For the 40 mg/ml strength the bioequivalence guideline does not give an exemption from the need to conduct in vivo studies as this strength differs in concentration of the active substance/excipients from the reference product and is administered by the SC or IM routes. Hence, it is not possible to assume bioequivalence of the 40 mg/ml strength for intramuscular use in pigs and subcutaneous use in cattle with the reference product. Therefore, no conclusions can be drawn in regard of the efficacy in both species cattle and pigs after SC and IM administration, respectively.

A target animal tolerance study with the 40 mg/ml strength in pigs showed that this strength is well tolerated. No target animal tolerance study was provided for subcutaneous use in cattle which was considered not acceptable.

Consequently, subcutaneous use in cattle and target species pigs were withdrawn for Meloxidolor 40 mg/ml. The SPC was amended accordingly.

In terms of the intravenous use of 40 mg/ml in cattle and horses the exemption of in vivo bioequivalence studies is acceptable according paragraph 7.1.a) of the bioequivalence guideline. It is accepted that the efficacy and the tolerance profile of Meloxidolor 40 mg/ml for horses and cattle will be the same as for the reference product when administered intravenously.

Part 5 – Benefit-risk assessment

Introduction

This application has been made in accordance with Article 13(3) of Directive 2001/82/EC, as amended (a hybrid application). The chosen reference products are Metacam 5 mg/ml solution for injection in dogs and cats, Metacam 5 mg/ml solution for injection in dogs and cats and Metacam 20 mg/ml solution for injection for cattle, pigs and horses.

The product was developed to closely resemble the formulations of the originator products. However, the Meloxidolor 40 mg/ml strength contains the double quantity of the active substance meloxicam and the excipient meglumine compared to the reference product Metacam 20 mg/ml. Due to lack of data the indications of Meloxidolor 40 mg/ml are limited to intravenous use in cattle and horses only and therefore differ from those of the respective reference product.

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. It is beneficial in the alleviation of inflammation and pain in both acute and chronic musculoskeletal disorders in a number of species, including dogs, cats, cattle, pigs and horses.

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

Additional benefits may be considered to arise from the reduction in severity of inflammation and pain in the agreed indications. The Meloxidolor 40 mg/ml presentation, which is for intravenous use, provides for a solution for injection with a 50% lower volume compared to a meloxicam 20 mg/ml solution. Unexpected adverse events with respect to local and systemic tolerance are not to be expected.

Risk assessment

It is accepted that the product will represent the same risks to target animals, users, consumer and environment as those for the reference products when used in accordance with label instructions.

However, in addition a possible risk to pregnant women and women of childbearing potential was identified due to the embryotoxic and reprotoxic potential of meloxicam.

Risk management or mitigation measures

The same appropriate sentences as for the reference products are included in the SPC and product information to prevent risks for the target animals, the user and for the environment. In addition the following warning is included to prevent a possible risk to the user: "*Meloxicam may be harmful for the foetus and unborn child. Pregnant women and women of child-bearing potential should not administer this product.*"

The same withdrawal periods as those of the reference product can be applied to Meloxidolor to ensure the safety for the consumer.

Evaluation of the benefit-risk balance

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

Meloxidolor 5 mg/ml solution for injection for dogs, cats, cattle and pigs and Meloxidolor 20 mg/ml solution for injection for cattle, pigs and horses are considered bioequivalent with the respective reference products on basis of their composition and proposed routes of administration. For the 40 mg/ml strength bioequivalence with the reference product was considered for intravenous administration in cattle and horses only.

The formulation and manufacture of Meloxidolor is well described and specifications set will ensure that product of consistent quality will be produced.

The tolerance and safety profiles are expected to be the same as for the respective reference products; 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. The same withdrawal periods as for Metacam 5 mg/ml and 20 mg/ml solution for injection in cattle, pigs and horses are retained.

Conclusion

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 Meloxidolor (5 mg/ml solution

for injection for dogs, cats, cattle and pigs, 20 mg/ml solution for injection for cattle, pigs and horses, 40 mg/ml solution for injection for cattle and horses) are considered to be in accordance with the requirements of Directive 2001/82/EC, as amended. The overall benefit-risk evaluation is deemed positive with a sufficiently clear and complete SPC and product literature.