Annex I

List of the name, pharmaceutical form, strength of the veterinary medicinal product, animal species, route of administration, applicant in the Member States

Member State EU/EEA	Applicant	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Austria	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 D-31303 Burgdorf Germany	Melosolute 40 mg/ml solution for injection for cattle, pigs and horses	meloxicam	Solution for injection	40 mg/ml	Cattle, pigs and horses	Cattle and horses – intravenous Pigs - intramuscular
Belgium	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 D-31303 Burgdorf Germany	Melosolute 40 mg/ml solution for injection for cattle, pigs and horses	meloxicam	Solution for injection	40 mg/ml	Cattle, pigs and horses	Cattle and horses – intravenous Pigs - intramuscular
Czech republic	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 D-31303 Burgdorf Germany	Melosolute 40 mg/ml solution for injection for cattle, pigs and horses	meloxicam	Solution for injection	40 mg/ml	Cattle, pigs and horses	Cattle and horses – intravenous Pigs - intramuscular
Denmark	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 D-31303 Burgdorf Germany	Melosolute 40 mg/ml solution for injection for cattle, pigs and horses	meloxicam	Solution for injection	40 mg/ml	Cattle, pigs and horses	Cattle and horses – intravenous Pigs - intramuscular
France	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 D-31303 Burgdorf Germany	Melosolute 40 mg/ml solution for injection for cattle, pigs and horses	meloxicam	Solution for injection	40 mg/ml	Cattle, pigs and horses	Cattle and horses – intravenous Pigs - intramuscular
Germany	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 D-31303 Burgdorf Germany	Melosolute 40 mg/ml solution for injection for cattle, pigs and horses	meloxicam	Solution for injection	40 mg/ml	Cattle, pigs and horses	Cattle and horses – intravenous Pigs - intramuscular

Member State EU/EEA	Applicant	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Hungary	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 D-31303 Burgdorf Germany	Melosolute 40 mg/ml solution for injection for cattle, pigs and horses	meloxicam	Solution for injection	40 mg/ml	Cattle, pigs and horses	Cattle and horses – intravenous Pigs - intramuscular
Ireland	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 D-31303 Burgdorf Germany	Melosolute 40 mg/ml solution for injection for cattle, pigs and horses	meloxicam	Solution for injection	40 mg/ml	Cattle, pigs and horses	Cattle and horses – intravenous Pigs - intramuscular
Italy	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 D-31303 Burgdorf Germany	Melosolute 40 mg/ml solution for injection for cattle, pigs and horses	meloxicam	Solution for injection	40 mg/ml	Cattle, pigs and horses	Cattle and horses – intravenous Pigs - intramuscular
The Netherlands	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 D-31303 Burgdorf Germany	Melosolute 40 mg/ml solution for injection for cattle, pigs and horses	meloxicam	Solution for injection	40 mg/ml	Cattle, pigs and horses	Cattle and horses – intravenous Pigs - intramuscular
Poland	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 D-31303 Burgdorf Germany	Melosolute 40 mg/ml solution for injection for cattle, pigs and horses	meloxicam	Solution for injection	40 mg/ml	Cattle, pigs and horses	Cattle and horses – intravenous Pigs - intramuscular
Spain	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 D-31303 Burgdorf Germany	Melosolute 40 mg/ml solution for injection for cattle, pigs and horses	meloxicam	Solution for injection	40 mg/ml	Cattle, pigs and horses	Cattle and horses – intravenous Pigs - intramuscular

Member State EU/EEA	Applicant	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
United Kingdom	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 D-31303 Burgdorf Germany	Melosolute 40 mg/ml solution for injection for cattle, pigs and horses	meloxicam	Solution for injection	40 mg/ml	Cattle, pigs and horses	Cattle and horses – intravenous Pigs - intramuscular

Annex II

Scientific conclusions and grounds for refusal of the granting of the marketing authorisation

Overall summary of the scientific evaluation of Melosolute 40 mg/ml solution for injection

1. Introduction

Melosolute 40 mg/ml solution for injection for cattle, pigs and horses contains meloxicam as active ingredient. Meloxicam is a Non-Steroidal Anti-Inflammatory Drug (NSAID) of the oxicam class which acts by inhibition of prostaglandin synthesis, thereby exerting anti-inflammatory, anti-exudative, analgesic and antipyretic effects. It also has anti-endotoxic properties which inhibit production of thromboxane B_2 induced by *E. coli* endotoxin administration in calves, lactating cows and pigs. The active substance is included in veterinary medicinal products currently authorised in the European Union via the centralised authorisation procedure, as well as nationally, for use in cattle, pigs, horses, dogs and cats. The proposed indications in cattle, pigs and horses for Melosolute 40 mg/ml are identical to the approved indications for the reference product, Metacam 20 mg/ml solution for injection for cattle, pigs and horses. Melosolute differs from the reference product through different strength of the active substance, meloxicam (40 mg/ml *versus* 20 mg/ml) and a different concentration of one of the excipients.

The applicant submitted an application for a decentralised procedure for Melosolute 40 mg/ml solution for injection for cattle, pigs and horses. This is a 'hybrid' application according to Article 13(3) Directive 2001/82/EC, as amended, referring to the centrally authorised reference product Metacam 20 mg/ml solution for injection for cattle, pigs and horses (EU/2/97/004). The reference Member State (RMS) is the Netherlands and 12 concerned Member States (CMS) are involved: Austria, Belgium, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Italy, Poland, Spain and the United Kingdom.

Melosolute 40 mg/ml solution for injection is administered intramuscularly in pigs, whereas in cattle and horses it is administered intravenously. Agreement was reached during the decentralised procedure with regard to data submitted to support the safety and the efficacy concerning target species cattle and horses. It should be noted that for cattle and horses, the applicant is exempt from providing an *in vivo* bioequivalence study under waiver 7.1.a of the CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2)[1] (Bioequivalence GL).

Potential serious risks were identified during the decentralised procedure by Ireland and the United Kingdom as they considered the bioequivalence of Melosolute 40 mg/ml solution for injection with the reference product, Metacam 20 mg/ml solution for injection had not been sufficiently demonstrated for the target species pigs, and no other satisfactory data had been provided to enable extrapolation of safety and efficacy data from the reference product for this species. These issues remained unsolved and therefore a referral under Article 33(1) of Directive 2001/82/EC to the CMD(v) was started. The Member States concerned failed to reach an agreement regarding the product and consequently the matter was referred to the CVMP on 29 June 2012.

This referral under Article 33(4) of Directive 2001/82/EC was made due to concerns that the applicant had not satisfactorily demonstrated the bioequivalence of Melosolute 40 mg/ml solution for injection with the reference product, Metacam 20 mg/ml solution for injection for the target species pigs, or provided other satisfactory justification to extrapolate the data of the reference product.

[1] EMA CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/04/WC500105372.pdf

2. Assessment of the data submitted

In order to address the concerns raised by the referral, the applicant presented a justification for the omission of a bioequivalence study for Melosolute 40 mg/ml solution for injection and the reference product, Metacam 20 mg/ml solution for injection. Considering the data submitted, the Committee concluded as follows on issues raised in the notification received from the Netherlands.

2.1. Bioequivalence between the test product and the originator

The Committee considered whether the bioequivalence of the test product with the reference product in the target species pigs had been proven, based on the available data.

This is a generic 'hybrid' application in which the applicant is extrapolating pre-clinical and clinical data from the reference product Metacam 20 mg/ml. In order to do this, the applicant must establish a link between the test and reference products and as the product is systemically active, the assumptions behind the concept of bioequivalence would allow this. This is the standard approach that has been applied in the past for intramuscularly or subcutaneously administered injections when the concentration of the active substance is changed, and it would be possible and scientifically valid for the applicant to conduct a comparative pharmacokinetic study to compare the Melosolute 40 mg/ml formulation with the Metacam 20 mg/ml formulation. In instances where it is not possible or scientifically relevant to conduct a blood-level bioequivalence/pharmacokinetic study, then alternative means (such as clinical end point studies) have to be used to demonstrate therapeutic equivalence.

The applicant considered it is not necessary to prove bioequivalence for this hybrid application but that a justification of therapeutic equivalence is sufficient. This justification is based on the following arguments:

- The pharmaceutical similarity of Melosolute 40 mg/ml and Metacam 20 mg/ml formulations. The test and reference products are qualitatively identical aqueous solutions, which differ only in the concentration of meloxicam and one of the excipients.
- Residues studies would suffice as a substitute for bioequivalence, considering that as the meloxicam residues in liver and muscle were comparable at the 4 hour sampling point and as the withdrawal times for Melosolute 40 mg/ml and Metacam 20 mg/ml are the same, the pharmacokinetic parameters will be comparable.
- Even if the formulations were inequivalent, the lack of bioequivalence would not be clinically relevant due to a wide therapeutic window. This was accepted by the Committee previously for the Metacam 5 mg/ml formulation.

The CVMP acknowledged the similarity of the formulations of the Melosolute 40 mg/ml and Metacam 20 mg/ml in terms of their excipients. However, the difference in concentration of the active substance also needs to be considered. Reports from literature suggest that the rate of absorption of a substance may be increased with decreased injection volume and increased concentration. This is supported by the evidence from the bioequivalence study between Metacam 5 mg/ml and Metacam 20 mg/ml which showed that C_{max} and AUC were higher for the higher concentration formulation, and the findings in residues studies that suggest more rapid absorption from the 40 mg/ml product. It is also noted that the Bioequivalence GL does not give an exemption from *in vivo* studies for solutions intended for parenteral injection where there is a difference in the concentration of the active substance.

The applicant has submitted a residue depletion study conducted with Melosolute 40 mg/ml as evidence of the comparative pharmacokinetic profile between their product and Metacam 20 mg/ml. The CVMP does not accept that the comparison of residues from two different products at a single time

point allows conclusions to be drawn about the blood concentration-time profile, or that the studies provide an accurate estimate of relative bioavailability.

Any increase in the rate/extent of absorption has not been quantified for Melosolute 40 mg/ml in a comparative pharmacokinetic study with the reference product and it could have implications in terms of target animal safety.

In conclusion, the applicant's arguments are not well set out. This is a 'hybrid' application and the requirements differ from those of a generic product due to the fact that the test formulation contains an increase in concentration of the active substance compared to the reference formulation. In this instance, the principles of bioequivalence would need to be applied to enable extrapolation of the safety and efficacy data from the reference product. The relevant guidance gives no exemption from the need to conduct *in vivo* bioequivalence studies for parenterally administered solutions when the strength of the active substance differs from that of the reference product and evidence suggests that this change does have the potential to influence the rate and possibly the extent of absorption. The applicant should have provided a blood-level comparative pharmacokinetic study between Melosolute 40 mg/ml and the reference product. This is the standard that has been generally requested from applicants seeking to change the strength of an injectable formulation (other than for intravenous route). In the absence of such a study, the residues depletion data provide no firm evidence that allows quantification of any difference in rate and extent of absorption of meloxicam between Melosolute 40 mg/ml and Metacam 20 mg/ml, and consequently the identification of its impact on clinical safety and efficacy is not possible. Therefore the applicant has not provided satisfactory data in pigs to enable extrapolation of the safety and efficacy data from the Metacam 20 mg/ml product and to allow this species to be included in the product information.

2.2. Relevance of the results from a residue depletion study as a demonstration of bioequivalence

The Committee considered if the results from a residue depletion study may be used as a surrogate for data from a bioequivalence study.

In the CVMP list of questions, the applicant was requested to address (i) the effect of comparing results from separately conducted studies, (ii) the effect that the number of animals sampled has on the reliability of the results (taking into account that for a standard bioequivalence study the test/reference ratio of the pivotal parameters must fall within predefined statistical limits); (iii) the timing and number of sampling points and how this relates to characterisation of the rate and extent of absorption; and (iv) how meloxicam concentrations in the tissues sampled (liver, kidney, muscle and injection site) relate to plasma pharmacokinetics.

I. Effect of comparing results from separately conducted studies

The applicant has provided references that broadly show comparability of pharmacokinetic data derived in studies conducted at different times. Some differences in pharmacokinetic parameters are attributed to different size/age of animal. However, for regulatory approval of a generic/hybrid product where the purpose of the study is to show any formulation effects, it is expected that comparative pharmacokinetic data would be collected from a single study with controlled study conditions (e.g. sampling methods, analytical methods, homogenous animal group) to minimise the effect of other variables. The provided data are not sufficient to assure that study conditions have negligible influence on the data to the level required for this type of regulatory submission.

II. Effect that the number of animals sampled has on the reliability of the results (taking into account that for a standard bioequivalence study the test: reference ratio of the pivotal parameters must fall within predefined statistical limits.)

The applicant did not comment on the level of confidence that can be attained with the results of the residues study. An insufficient number of animals was used in each of the residues studies to achieve the required precision. This was clear from the variability shown in the data and referred to by the applicant.

III. Timing and number of sampling points and how this relates to characterisation of the rate and extent of absorption and IV. Meloxicam concentrations in the tissues sampled (liver, kidney, muscle and injection site) and their relation to plasma pharmacokinetics.

These points were addressed together. The applicant accepted the timing and number of sampling points required for bioequivalence and residues depletion studies are very different, according to the respective guidelines. However, the applicant claims there is a very fast distribution of meloxicam from the intramuscular injection site into the general circulation and subsequently a very fast elimination from tissues like liver, kidney and muscle taking into consideration the identical elimination half-life in pigs after intravenous or intramuscular administration, which justifies the claim for waiver of a bioequivalence study in pigs based on results of the residue depletion study in comparison to the Metacam 20 mg/ml product.

The CVMP considers that the purpose and design of bioequivalence and residues studies are very different. The presented studies evaluate the depletion of tissue residues following the administration of the products in the target species using the recommended or proposed dose rate and route of administration, with the purpose of determining when these fall below the MRLs. Both studies showed that meloxicam is rapidly eliminated from the tissues of the pig, falling below MRL in most tissues within a day of administration. However, in a bioequivalence study, the principle is that blood concentrations are determined over a certain timeframe, critically including the absorption phase, to derive an estimate of C_{max} and AUC with the knowledge that these correlate with therapeutic effect. It is noticed that peak plasma concentration was reached 1 hour after the second administration in the residue depletion study using ^{14}C-Meloxicam 20 mg/ml and declined rapidly from a C_{max} of 1730 ng equivalent/ml at 1 hour after administration and over the next 95 hours (no sampling time points stated). The tissue concentration levels were derived from samples taken at 4 hours and at 2, 4 and 8 days (20 mg/ml study) or 1, 3 and 5 days after the final administration (40 mg/ml study). The timing and sparsity of sampling of tissues does not allow tissue residue concentrations to be used as a surrogate for plasma levels that would allow an estimation of blood C_{max} and AUC. Meloxicam appeared to be more rapidly absorbed from the 40 mg/ml compared to the 20 mg/ml injection site, as suggested from the residue depletion data at the first (4 hours) sampling time-point, where the injection site levels were lower and kidney levels higher for the 40 mg/ml formulation. Although meloxicam levels in liver and muscle tissue are similar at the 4 hours sampling for both products, this reflects a single time point and gives no indication of whether plasma levels would be similar throughout the duration of the blood level concentration-time curve.

In conclusion, the following points were not adequately addressed by the applicant: (i) the impact of using different studies for comparison of formulation effects, (ii) the choice of time points which are not consistent with the absorption phase, and do not provide evidence of the rate and extent of absorption (iii) the robustness of the data in relation to the precision of the estimates needed to provide accurate comparison between formulations.

3. Benefit-risk assessment

Introduction

Melosolute 40 mg/ml solution for injection for cattle, pigs and horses contains meloxicam 40 mg/ml. The application was submitted as a generic hybrid application under Article 13(3), as there is currently no authorised product with the same concentration of meloxicam.

Direct therapeutic benefit

Meloxicam is a NSAID of the oxicam class which acts by inhibition of prostaglandin synthesis, thereby exerting anti-inflammatory, anti-exudative, analgesic and antipyretic effects. It also has anti-endotoxic properties which inhibit production of thromboxane B_2 induced by *E. coli* endotoxin administration in calves, lactating cows and pigs.

- In cattle, the proposed indications are for use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs; for use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and in young, non-lactating cattle, and for adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy.
- In pigs, the proposed indications are for use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation, and for adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy.
- In horses, the proposed indications are for the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders and for the relief of pain associated with equine colic.

For this generic 'hybrid' application, the benefits are extrapolated from the safety and efficacy data for the reference product, Metacam 20 mg/ml. For horses and cattle the aqueous solution is administered via the intravenous route, therefore bioequivalence can be accepted as self-evident. However, for pigs, where the product is administered intramuscularly, the applicant has not provided sufficient evidence of the relative rate and extent of absorption, to allow extrapolation of the data from the reference product.

Risk assessment

While there is a theoretical risk of increased inflammation at the site of injection due to increased tonicity of the 40 mg/ml formulation compared with the lower concentration of the reference product, injection site clinical observations and gross and microscopic pathology conducted during the residues study indicated that local inflammatory responses were minimal. The main remaining risk arises from the uncertainty due to lack of data on the pharmacokinetic profile and exposure to meloxicam following intramuscular injection of the 40 mg/ml test product in pigs. Hence, the safety and efficacy of the product remains unknown for pigs.

Evaluation of the benefit-risk balance

The benefit-risk balance for pigs remains inconclusive in absence of adequate information on the safety and efficacy of the product.

Conclusion

Based on the data presented and the responses to questions, the CVMP concluded that the data for Melosolute 40 mg/ml solution for injection for cattle, pigs and horses were not in accordance with the requirements of Directive 2001/82/EC, and that the benefit-risk balance is currently not favourable with respect to its proposed indications in the target species pigs.

Grounds for the refusal of the granting of marketing authorisations for the target species pigs

Having considered all data submitted the CVMP concluded that:

- as this is a generic 'hybrid' application, in the absence of other data the principles of bioequivalence would need to be applied to determine the expected safety and efficacy of the product by extrapolation of the pre-clinical and clinical data from the reference product. The current guideline on the conduct of bioequivalence studies (EMA/CVMP/016/00-Rev.2) gives no exemption from the need to conduct *in vivo* bioequivalence studies for parenterally administered solutions when the strength of the active substance differs from that of the reference product and evidence suggests that this change does have the potential to influence the rate and possibly the extent of absorption;
- the residues depletion data provided no firm evidence that allows quantification of any difference in rate and extent of absorption of meloxicam between Melosolute 40 mg/ml and Metacam 20 mg/ml, and therefore to quantify its impact on clinical safety and efficacy;

the particulars concerning the target species pigs that were submitted in support of the application do not comply with Article 13 of Directive 2001/82/EC, and consequently do not satisfy the criteria for authorisation in respect of safety and efficacy for the target species pigs. Therefore the CVMP recommends the refusal of the granting of the marketing authorisation for Melosolute 40 mg/ml solution for injection for the target species pigs.

Annex III

Amendments in the relevant sections of the summary of product characteristics, labelling and package leaflet

All references to the target species pigs should be removed from the final versions of the summary of product characteristics, labelling and package leaflet agreed during the Coordination group procedure.