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Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Contacera (EMEA/V/C/002612)

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 the granting of a community marketing authorisation of Contacera was submitted to the Agency on 28 September 2011 by Pfizer Limited. This application is submitted under Article 3(3) of Regulation (EC) No 726/2004 in accordance with Article 13(1) of Directive 2001/82/EC as amended (a generic application).

The CVMP adopted an opinion and CVMP assessment report on 11 October 2012.

On 6 December 2012, the European Commission adopted a Commission Decision for this application.

Contacera contains meloxicam (a NSAID) as active ingredient at a concentration of 20 mg/ml. The target species are cattle, horses and pigs. The route of administration in cattle is subcutaneous, intravenous in horses and intramuscular in pigs.

The product was developed in such a way as to closely resemble the formulation of the originator product, Metacam 20 mg/ml solution for injection for use in cattle, pigs and horses.

The proposed indications are identical to those included in the SPC of the reference product, namely:

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

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

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

Part 1 - Administrative particulars

The three manufacturing sites of the finished product Chanelle Pharmaceuticals Manufacturing Ltd., Eurovet Animal Health B.V. and bela-pharm GmbH & Co. KG are both located within the EU and are appropriately authorised for the manufacture of the product in accordance with EU Good Manufacturing Practice (GMP). GMP certificates, dated May 2011, January 2010 and August 2009, were provided for Chanelle, Eurovet and bela-pharm, respectively.

For the active substance an active substance master file (ASMF) was provided. The manufacturer and AMSF holder Amsa S.p.A. is located in Italy. The manufacturing authorisation and the GMP status are adequately documented and acceptable.

No inspections are requested.

Detailed description of the pharmacovigilance system

The description of the Pfizer Animal Health pharmacovigilance system (version 15) is in line with the current regulations and it is considered to fulfil the requirements of the current legislation of the European Union.

Part 2 - Quality

Composition

Contacera contains 20 mg/ml of meloxicam as active ingredient and 159.8 mg/ml of ethanol (96%) as antimicrobial preservative. The excipients are meglumine, Macrogol 400, Poloxamer 188, glycine, disodium edetate, sodium hydroxide, hydrochloric acid, water for injections and nitrogen. The only difference in the composition of Contacera compared to the reference product is the replacement of Macrogol 300 by Macrogol 400. It was proven that this difference has no influence on the viscosity of the product, compared to the reference product.

Container

The product is presented in type I clear glass vials, closed with a type I bromobutyl rubber stopper and an aluminium cap. Pack sizes are 20 ml, 50 ml, 100 ml and 250 ml.

Development pharmaceutics

Contacera has been formulated to be pharmaceutically similar to the reference product. The product has comparable physical characteristics to the reference product, i.e. appearance, pH and viscosity.

Method of manufacture

The typical batch size will vary from 250 l to 2500 l. The manufacturing process consists of mixing ingredients, adjusting the pH of the obtained solution, filtering the solution, filling the solution in vials and sterilising the filled vials at 121 °C for 15 minutes.

The finished product is manufactured according to a standard process in which the in-process controls are planned at three steps: preparation of the ingredients, filtration of the solution and filling of the vials. The description of the manufacturing process and the proposed in-process controls are satisfactory.

The validation of the manufacturing process has been conducted on two industrial-size batches (500 l). The data provided on validation is acceptable and therefore, the manufacturing process of the finished product Contacera is considered validated.

Control of starting materials

Active substance

The active substance, meloxicam is described in the European Pharmacopoeia (Ph. Eur.). An active substance master file (ASMF) is provided for meloxicam sourced from the manufacturer AMSA S.p.A. in Italy. The active substance was demonstrated to comply with the current Ph. Eur. monograph for meloxicam and the data provided in the ASMF (in both the 'Open' and 'Restricted' parts) are acceptable.

Excipients

All of the excipients are described in the Ph. Eur. and they are controlled according to their corresponding monograph. The relevant certificates of analysis issued by the applicant and suppliers of excipients have been provided.

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 on the finished product

The specifications proposed at release and at the end of shelf-life are basically appropriate to control the quality of the finished product as they comply with the VICH requirements.

The description and the validation of the methods used for the control of the finished product were provided and considered acceptable. The results of the analysis of finished product are presented and comply with the required VICH specifications.

Stability

The proposed retest period for the active substance is 5 years, stored in polyethylene bags in fibre drums. Results from storage of batches of the substance for up to 60 months at 25 °C/60% RH, and for 6 months at 40 °C/75% RH are available. No relevant changes were observed. The proposed retest period is considered acceptable.

The proposed shelf-life of 3 years for finished product, based on the presented stability test results, is accepted.

The photostability study shows a slight degradation of the finished product for vials directly exposed to light for 10 hours. However the absence of the precaution "Keep vial in the outer carton" in section 6.4 of the SPC is accepted since the increase of the impurities during the photostability study is only slight and the content of these impurities in the finished product remain within their specifications.

The proposed in-use shelf-life of 28 days is accepted. Repeated in-use stability tests on batches of the finished product at the end of its shelf-life confirm the in-use shelf-life.

Overall conclusion on quality

The data provided in part 2 of the dossier are in line with VICH requirements and are acceptable. The product is a simple solution for injection which utilises standard pharmaceutical excipients. The active substance is monographed in the European Pharmacopoeia; both active substance and formulated product appear stable.

Part 3 – Safety

Safety documentation

This application is made in accordance with Article 13(1)(a) (iii) of Directive 2001/82/EC, as amended. As bioequivalence was established between Contacera and the reference product (see part 4 of this report) the results of toxicological and pharmacological tests and clinical trials were not required.

Studies of other effects

All excipients used in the formulation of Contacera 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.

User safety

The applicant has provided a user risk assessment that was conducted in accordance with the current guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1).

Given that the limited difference of formulation between the product and the reference product has not impact on the absorption of the product, that the excipients included in the formulations have a well-know toxicological profile and that therapeutic schemes and indications are identical to those of the reference product, it can be expected that the potential hazard to the user posed by Contacera will be the same as posed by the reference product. The proposed risk management sentences in the SPC are considered appropriate to ensure user safety.

Environmental risk assessment

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 a small number of 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 conclusion on the safety documentation

This is a generic application and the differences in composition between Contacera and the reference product are very limited. Given that both products are similar and all excipients have a well known toxicity profile, it is accepted that the potential risk to the user posed by Contacera will be that the same as posed by the reference product.

All excipients are commonly used in human and veterinary medicinal products and their toxicological profiles are well known. Therefore, it can be assumed that they will not raise a toxicological concern. The same warning sentences for the user as for the reference product will be included in the SPC which are adequate to ensure the safety of the person who will administer the product.

The product is not expected to pose a risk for the environment when used as recommended. The standard disposal advice as for the reference product will be included in the SPC.

Residues documentation

Residue studies

No new studies have been provided. See below.

Pharmacokinetics

No studies on pharmacokinetics were performed with Contacera.

Depletion of residues

Two confirmatory GLP residue depletion studies were performed with the 20 mg/ml presentation in order to determine the injection site residue depletion profile of the new product Contacera and to verify the residue levels.

The product was administered once subcutaneously in cattle at the recommended dose of 0.5 mg/kg bw and in pigs once intramuscularily at the recommended dose of 0.4 mg/kg bw.

In cattle injection side residue levels of meloxicam were below the Lower Limit of Quantification of the analytical method (5.0 µg/kg) from day 13 on; in pigs the residue levels were below the Limit of Detection (1.0 µg/kg) from day 4 on.

These two confirmatory GLP studies were satisfactorily performed except for the low bodyweight of animals (cattle: 280-334 kg, pigs: 40-48 kg).

Given that the only difference in formulation between Contacera and the reference product is the use of the diluent Macrogol 400 instead of Macrogol 300 which was proven to have no effect on viscosity of the product and therefore the product is considered bioequivalent with the reference procuct, the results of the residue depletion studies are not considered to be pivotal.

MRLs

The active substance in Contacera 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 Contacera is considered bioequivalent with the reference product (see part 4), the withdrawal periods (meat and offal and, where applicable, milk (cattle)) for Contacera are the same as the established withdrawal periods of the reference product. Contacera is not authorised for use in horses producing milk for human consumption.

Overall conclusion on the residue documentation

The established withdrawal periods of the reference product as listed below are applied for Contacera.

Cattle:

Meat and offal: 15 days

Milk: 5 days

Pigs:

Meat and offal: 5 days

Horses:

Meat and offal: 5 days.

The product is not authorised for the use in horses producing milk for human consumption.

Part 4 – Efficacy

The application for a marketing authorisation for Contacera is made in accordance with Article 13(1) (a) (iii) of Directive 2001/82/EC, as amended (a generic). The reference product is Metacam 20 mg/ml solution for cattle, pigs and horses.

No *in vivo* bioequivalence studies were performed but an acceptable justification to waive the requirement was given.

For horses, the waiver of a bioequivalence study is acceptable according to point 7.1a) of the bioequivalence guideline (EMA/CVMP/016/00-Rev.2) as the product is to be administered solely as an aqueous intravenous solution containing the same active substance as the reference product.

The route of administration in cattle and pigs is subcutaneous and intramuscular, respectively. The formulation of both Contacera and the reference product are similar, with one exception that Macrogol 300 was replaced by Macrogol 400. A comparative viscosity study showed that the difference in the relative molecular mass of Macrogol 300 and Macrogol 400 has no influence on the viscosity of the product. As the limited difference of the formulation has no impact on the viscosity of Contacera compared to the reference product it can be concluded that the absorption of the product is comparable to that of the reference product and bioequivalence can be assumed.
Therefore, a waiver of bioequivalence studies in cattle and pigs is acceptable according to point 7.1b) of the bioequivalence guideline (EMA/CVMP/016/00-Rev.2) as it was adequately justified that the difference in the excipients has no influence on the rate and/or extent of absorption of the active substance.

Contacera is considered bioequivalent with the reference product.

Pharmacodynamics

Some published studies were 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 Contacera and the reference product, the sections 5.1 and 4.2 of the SPC of Contacera are the identical to those of the reference product.

Target animal tolerance

The local tolerance of the product was followed in the residue depletion studies conducted in cattle and pigs after subcutaneous and intramuscular injection, respectively. From these studies it can be concluded that at the recommended dose, the product is well tolerated in these species.

No tolerance studies in horses were provided. As the product is administered in horses intravenously and as it was shown that the limited difference of formulation has no impact on the absorption of the

product, it is estimated that the tolerance profile of Contacera will be the same as for the reference product. Consequently it can be concluded that at the recommended dose the product is well tolerated in horses.

As bioequivalence between Contacera and the reference product was established, the expected tolerance profile of Contacera in the field is the same as for the reference product.

Field trials

Not applicable for this type of application, considering that bioequivalence has been established with the reference product.

Overall conclusion on efficacy

This is a generic application for a marketing authorisation in accordance with Article 13(1)(a)(iii) of Directive 2001/82/EC, as amended. The cited reference product is Metacam 20 mg/ml solution for injection.

The formulation of Contacera is considered similar to the reference product with a difference concerning one excipient. A comparative viscosity study showed that this difference has no influence on the rate and extent of absorption of the active substance. Hence, the waiver of bioequivalence studies is accepted and bioequivalence is considered established.

As the excipients of the product are not expected to raise toxicological concerns for the animal safety, no specific tolerance studies, in order to determine margins of safety in the target species, are required.

Given that bioequivalence of Contacera with the reference product is established, it is accepted that the efficacy and the clinical tolerance of the test will be the same as for the reference product.

Part 5 – Benefit risk assessment

Introduction

The application for Contacera is a generic application. The product was developed in such a way as to closely resemble the formulation of the originator product, Metacam 20 mg/ml solution for injection for use in cattle, pigs and horses.

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 cyclo-oxygenases 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 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.

Risk assessment

It is accepted that the product does not represent an unacceptable risk to users or the environment when used in accordance with label instructions. The risk for environment and consumer is considered to be the same as that for the reference product.

Risk management or mitigation measures

Appropriate sentences are included in the SPC and product information to prevent risks for the user and for the environment. Withdrawal periods, identical to those of the reference product, have been retained.

Evaluation of the benefit risk balance

The only difference in formulation between Contacera and the reference product is the use of the diluent Macrogol 400 instead of Macrogol 300, which is proven to have no effect on viscosity of the product. The exemption from conducting bioequivalence studies *in vivo* is considered acceptable. The withdrawal periods for meat/offal and milk, where appropriate, are same in all species as for Metacam 20 mg/ml solution for injection in cattle, pigs and horses.

Conclusion

The overall benefit-risk balance is deemed positive.

Based on the original and complementary data presented, it is concluded that the quality, safety, and efficacy of Contacera were considered to be in accordance with the requirements of Directive 2001/82/EC, as amended.