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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Contacera (EMEA/V/C/002612/X/0002)

International non-proprietary name: Meloxicam

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Introduction

An application for an extension to the Community marketing authorisation for Contacera was submitted by Pfizer Limited to the European Medicines Agency (the Agency) on 5 March 2013 in accordance with Article 19 of Commission Regulation (EC) No. 1234/2008 and Annex I point 2 thereof. The rapporteur appointed was M. Holzhauser-Alberti and co-rapporteur W. Schlumbohm.

Contacera 20 mg/ml suspension for injection for cattle, pigs and horses was granted a marketing authorisation by the European Commission on 6 December 2012.

This extension application is to add a new pharmaceutical form and a new strength meloxicam 15 mg/ml oral suspension for the existing target species horses for Contacera. The new formulation is intended for administration by a new route of administration (oral). The reference product is Metacam 15 mg/ml oral suspension for horses.

The target species is horses. The route of administration is oral use.

The proposed indication is "alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses".

The proposed withdrawal period for meat and offal is 3 days. The product is not authorised for use in lactating animals producing milk for human consumption.

Contacera 15 mg/ml oral suspension is available in high-density polyethylene (HDPE) bottles containing 100 or 250 ml with a tamper proof child resistant closure and together with a polypropylene measuring syringe in a cardboard box.

The CVMP adopted an opinion and CVMP assessment report on 12 December 2013.

On 13 February 2014, the European Commission adopted a Commission Decision for this application.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the pharmacovigilance system (8 March 2011) was submitted 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 European Union or in a third country.

Manufacturing authorisations and inspection status

The finished product is manufactured by Chanelle Pharmaceuticals Manufacturing in Ireland who is appropriately authorised for the manufacture of the product in accordance with EU Good Manufacturing Practice (GMP); a GMP certificate was provided. Secondary packaging and batch release for the EU will be carried out by the same manufacturer.

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

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certifications of the manufacturing sites were considered in line with legal requirements.

Part 2 - Quality

Composition

Contacera 15 mg/ml oral suspension for horses has been formulated to be essentially similar to Metacam 15 mg/ml oral suspension. Both contain the active ingredient meloxicam in the same concentration. The formulation also includes the following excipients which are the same as for the reference product: saccharin sodium, carmellose sodium (carboxymethylcellulose), silica colloidal anhydrous, citric acid monohydrate, sorbitol, honey aroma, disodium phosphate dodecahydrate and purified water.

The difference in the formulation compared to the reference product consists of a different quantity of sodium benzoate, the omission of xylitol and glycerol and the use of carboxymethylcellulose and disodium phosphate dodecahydrate, instead of hydroxyethylcellulose and sodium dihydrogenphosphate dihydrate, respectively.

Container

The product is presented in HDPE bottles of 100 and 250 ml in a cardboard box together with a measuring syringe. The applicant has demonstrated that a reproducible and accurate dose of the product is delivered with the measuring syringe under testing conditions which take due account of the range of the proposed dosage regimen.

Development pharmaceutics

Contacera 15 mg/ml oral suspension for horses has been formulated to be essentially similar to the reference product Metacam 15 mg/ml oral suspension for horses.

The anti-microbial preservative efficacy testing has been performed according to the European Pharmacopoeia (Ph. Eur.) and shows a satisfactory antimicrobial efficacy of sodium benzoate in the finished product at the low limit (0.45%).

Method of manufacture

The finished product is manufactured at Chanelle Pharmaceuticals Manufacturing in Ireland according to a standard process with appropriate in-process controls monitoring the reproducibility of the manufacture. The description of the manufacturing process and the proposed in-process controls are satisfactory.

The validation of the manufacturing process has been satisfactorily conducted on two industrial batches (on the lowest industrial size batch).

Control of starting materials

Active substance

The active substance, meloxicam, is described in the Ph. Eur. Data for meloxicam are submitted in an active substance master file which has been assessed for the initial marketing authorisation of Contacera.

Excipients

All excipients are described in the Ph. Eur. except the honey aroma for which supplier's data on its composition and origin are provided. The information provided on the honey aroma is considered satisfactory.

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 (EMEA/410/01 rev.3).

Control tests during production

The in-process controls are specified in the description of the manufacturing process and are considered satisfactory.

Control tests on the finished product

The specifications of the finished product are considered acceptable for this type of dosage form (e.g. active substance assay, preservative assay, particle size analysis, microbiological quality). The impurity determination is only included in the shelf-life specification and not in the release specification. Control tests are performed according to the Ph. Eur. methods. The control methods used in the control of the finished product are well validated and considered acceptable.

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 (relative humidity), at 30 °C/70% RH and for 6 months at 40 °C/75% RH are available. No relevant changes were observed. The proposed retest period is considered acceptable.

Results from long-term and accelerated stability studies of the finished product were presented. Two production scale batches were stored for 24 and 36 months at 25 °C/60% RH and for 6 months at 40 °C/75% RH. The results demonstrate the product to be stable. The data are considered sufficient to support the proposed shelf life of 3 years.

No photostability study is presented, however as the suspension is presented in opaque containers this is considered acceptable. No freeze-thaw study is presented in the dossier, therefore the precaution *Do*

not freeze, should be added in the special storage conditions of the summary of product characteristics (SPC).

Results of an in-use stability study with one batch at 25 °C/60% RH over 3 months were presented in support of the proposed 3-months in-use stability. The in-use stability testing was repeated on a batch which was almost 4 years old. The data are considered sufficient to support the in-use stability of 3 months.

As the pharmaceutical form is a suspension, the particle size is a critical attribute which may potentially impact on bioavailability. Satisfactory specifications for particle size are given and meloxicam with a particle size of not less than 90% ≤ 10 µm is used in the manufacture of this product.

Overall conclusions on quality

The data provided in part 2 of the dossier are in line with the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) guidelines and are acceptable. The active substance is monographed in the Ph. Eur.; both active substance and formulated product appear stable. However, in absence of a freeze-thaw study, the precaution "Do not freeze" is included in section 6.4 of the SPC.

Shelf life and storage precautions supported by the stability studies:

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf life after first opening the immediate packaging: 3 months.

Do not freeze.

Part 3 – Safety

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 add a new strength meloxicam 15 mg/ml in a new pharmaceutical form (oral suspension) for the existing target species horses.

In support of this application, an in vivo bioequivalence study was provided with the reference product in horses (as described in part 4 of this report). Contacera 15 mg/ml was shown to be bioequivalent with the reference product at the proposed dose in horses.

Safety documentation

Pharmacology

No data in respect of pharmacology are provided. Given that bioequivalence of Contacera 15 mg/ml with Metacam 15 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 Contacera 15 mg/ml with Metacam 15 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.

User safety

A user safety assessment was conducted in accordance with the current Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1). The dermal route as a possible route of unintentional exposure cannot be ruled out, but this exposure has not been assessed here. However, bioequivalence is shown with Metacam oral suspension for horses and the excipients included in the formulations are considered safe. The information provided on honey flavour is considered appropriate and acceptable. The proposed posology and indications are identical to those of the reference product, therefore it is accepted that the potential hazard of Contacera oral suspension for horses will be the same as posed by the reference product. The inclusion of the same user safety statements in the SPC as those in the SPC of the reference product are considered appropriate.

Environmental risk assessment

The product is intended to be used in horses for the alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders.

A Phase I environmental risk assessment was provided in line with line with the VICH guideline GL6 - Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products (VMPs) - Phase I (CVMP/VICH/592/98-FINAL). Given that the product is for the treatment of an individual or a small number of animals in a flock or herd, the environmental risk assessment can stop at Phase I. Contacera 15 mg/ml oral suspension is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

The data for this application are provided in accordance with Article 13(1) of Directive 2001/82/EC (a generic application). Contacera 15 mg/ml oral suspension was shown to be bioequivalent with the reference product in an *in vivo* bioequivalence study as described in part 4 of this report. Therefore, it can be concluded that the safety profile of Contacera 15 mg/ml oral suspension will be the same as for the reference product.

As all excipients are commonly used in human and veterinary medicinal products and their toxicological profiles are well known, 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 according to the SPC.

Residues documentation

No residue depletion studies were provided. Given that bioequivalence was shown between Contacera 15 mg/ml oral suspension and Metacam 15 mg/ml oral suspension and the product is to be administered orally, no confirmatory local residue studies are required. According to the CVMP Note for guidance: Approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95-FINAL) and the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) confirmatory local residue studies are required only for parenterally administered products via intramuscular or subcutaneous route.

MRLs

The active substance(s) 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

Bioequivalence is demonstrated between Contacera 15 mg/ml oral suspension for horses and the reference product. The route of administration is oral. Therefore it is not necessary to perform confirmatory depletion studies. It is accepted that the established withdrawal period of the reference product will be retained for Contacera 15 mg/ml oral suspension for horses.

Meat and offal: 3 days.

The product is not authorised for use in lactating animals producing milk for human consumption.

Overall conclusions on the residues documentation

The proposed withdrawal period of:

- Meat and offal: 3 days.

Not authorised for use in lactating animals producing milk for human consumption can be accepted.

Part 4 – Efficacy

The data for this application are provided in accordance with Article 13.1(a)(iii) of Directive 2001/82/EC (generic application). This extension application is to add a new strength meloxicam 15 mg/ml in a new pharmaceutical form (oral suspension) for an existing target species horses.

In support of this application, the applicant provided an *in vivo* bioequivalence study in horses with the reference product. Contacera 15 mg/ml was shown to be bioequivalent with the reference product when administered orally in horses.

Pharmacodynamics

Peer-reviewed published literature was provided by the applicant to document the pharmacodynamic properties of the active substance, meloxicam which is considered as supportive information. As bioequivalence Contacera with the reference product was demonstrated (as described below), the pharmacodynamic properties are expected to be the same as those of the reference product and section 5.1 of the SPC of Contacera 15 mg/ml oral suspension is identical to that of the reference product.

Development of resistance

Not applicable.

Pharmacokinetics

Oral Bioequivalence Study of Meloxicam 15 mg/ml Suspension in Horses (Sedlak, 2009)

A good laboratory practice (GLP) compliant single dose, two period, two sequence cross-over bioequivalence study with a 14-day wash-out period was performed in horses in order to demonstrate bioequivalence between the proposed new formulation Contacera 15 mg/ml oral suspension for horses and the reference product Metacam 15 mg/ml following single oral administration of meloxicam at 0.6 mg/kg bodyweight (bw). The chosen wash out period of 14 days was in excess of ten half-lives for the active meloxicam in horses and is considered appropriate.

Twenty-four clinically healthy horses (Czech warm-blood, age 3.8–14.0 years, 414–610 kg bw) were randomly divided into two groups of 12 animals each (6 males and 6 females). At Day 0 the proposed new formulation was administered orally direct on the root of tongue to one group and Metacam 15 mg/ml to the second group at the recommended dose of 0.6 mg/kg bw. After a wash-out period of 14 days, the animals of both groups were cross-administered. 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 (80% – 125% for AUC, enlarged interval of 70% – 143% for C_{max}).

The 90% confidence intervals for AUC fell within the specified limits which, in accordance with the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) was considered demonstrative of bioequivalence. The enlarged interval for C_{max} was justified with the expected variability and is not expected to be crucial for the safety and efficacy of the oral therapy. The enlarged interval for C_{max} was considered acceptable.

During the study no disorders in the health status, occurrence of adverse events or other alterations were observed in the treated animals.

This study was correctly performed (design, target species, treatment). The analytical method used to assay meloxicam in plasma samples was correctly validated.

Based on the findings of the study, CVMP considers that bioequivalence was shown between Contacera 15 mg/ml and the reference product following oral administration to horses. Therefore, it

can be expected that the efficacy and the tolerance profile of Contacera is the same as that of the reference product.

It is considered appropriate that section 5.2 of the SPC of Contacera 15 mg/ml oral suspension for horses is identical to the SPC of Metacam 15 mg/ml oral suspension for horses.

Dose determination/justification

Not applicable.

Target animal tolerance

No standard tolerance study in the target species has been conducted. 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.

As bioequivalence of Contacera 15 mg/ml oral suspension for horses with Metacam 15 mg/ml oral suspension for horses was demonstrated, this is considered acceptable. Additionally, the bioequivalence study confirms that the product is well tolerated when administered orally at the proposed dose of 0.6 mg/kg bw.

Field trials

No studies were provided. Given the type of application (a generic) and the fact that Contacera 15 mg/ml suspension 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 an *in vivo* bioequivalence study was provided which showed that Contacera 15 mg/ml oral suspension is bioequivalent to the reference product Metacam 15 mg/ml oral suspension when administered orally to horses. Therefore it can be concluded that Contacera 15 mg/ml is expected to be as efficacious as the reference product and the systemic tolerance can be considered to be the same as the reference product.

Part 5 – Benefit-risk assessment

Introduction

The application for Contacera 15 mg/ml oral suspension for horses is an extension application to add a new strength and a new pharmaceutical form meloxicam 15 mg/ml oral suspension for an existing target species horses and the data are provided in accordance with Article 13(1) of Directive 2001/82/EC (a generic application).

The product was developed in such a way as to be essentially similar to the formulation of the reference product, Metacam 15 mg/ml oral suspension for horses.

The proposed indication is: Alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses.

The dossier has been submitted in accordance with Article 19 of Commission Regulation (EC) 1234/2008 and Annex I point 2 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. It is beneficial in the alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders in horses. Consequently it may be considered to benefit animal welfare and aid in the control of inflammatory symptoms associated with the disorders specified in section 4.2 of the SPC. It is expected that the product will have an acceptable safety profile in the target species when administered at the proposed treatment dose.

Additional benefits

The product is presented as an oral suspension with honey flavour for easy administration to horses.

Risk assessment

The formulation and the manufacture of Contacera 15 mg/ml are well described and specifications set will ensure that a product of consistent quality will be produced.

Since bioequivalence was demonstrated *in vivo* between the two products, Contacera 15 mg/ml oral suspension for horses is expected to be as safe and efficacious as the reference product Metacam 15 mg/ml oral suspension for horses. It is accepted that the product will represent the same risks to target animals, users, consumer and environment as those for the reference product when used in accordance with the SPC.

It is accepted that the withdrawal period is the same as that established for the reference product, i.e. meat and offal: 3 days. The product is not authorised for use in horses producing milk for human consumption.

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

Risk management or mitigation measures

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

Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall. Contacera 15 mg/ml oral suspension is expected to have the same efficacy as the reference products for the indications as stated in the SPC.

The formulation and manufacture of Contacera 15 mg/ml oral suspension is well-described and the specifications set will ensure that a product of consistent quality will be produced.

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

Conclusion

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

Based on the original and complementary data presented the CVMP concluded that the quality, safety and efficacy of Contacera 15 mg/ml oral suspension for horses are considered to be in accordance with the requirements of Directive 2001/82/EC.