10 January 2013
EMA/25130/2013
Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP Assessment Report for Loxicom (EMEA/V/C/000141/X/009)

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 8447
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

© European Medicines Agency, 2022. Reproduction is authorised provided the source is acknowledged.

Introduction

An application for an extension of a Community marketing authorisation of Loxicom was submitted to the European Medicines Agency (the Agency) on 26 October 2011 by Norbrook Laboratories Limited in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I thereof.

Loxicom was given a marketing authorisation by the European Commission on 10 February 2009.

The Loxicom product range comprises 0.5 mg mg/ml oral solution for dogs and cats, 1.5 mg/ml oral suspension for dogs, 5 mg/ml solution for injection for dogs and cats and 20 mg/ml injection for solution for cattle, pigs and horses.

This Loxicom extension concerns a new strength and a new pharmaceutical form meloxicam 50 mg/g oral paste for horses. It is presented in a low-density polyethylene syringe available in pack sizes of 1, 7 and 14 syringes. It is indicated for the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses. The route of administration is oral use. The target species is horses.

This application has been made in accordance with Article 13(3) of Directive 2001/82/EC, as amended (a hybrid application). The reference product cited by the applicant which has been authorised within the European Community is Metacam 15 mg/ml oral suspension for horses.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the pharmacovigilance system (version dated February 2011) was provided which fulfils the requirements of Directive 2001/82/EC, as amended. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Declarations of compliance of the manufacture of the product with EU GMP requirements have been provided. No inspections are considered necessary.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the finished product manufacturing and packaging sites are considered in line with legal requirements.

The active ingredient manufacturing site has been inspected by an EU competent authority, confirming the GMP status of this site.

Part 2 - Quality

Composition

The product is an aqueous oral paste containing the active substance meloxicam at a concentration of 50 mg/g and the preservative benzyl alcohol. The excipients used in the formulation are hydroxypropyl cellulose, glycerol, xanthan gum, sorbitol, benzyl alcohol, saccharin sodium and an apple flavouring agent.

Container

The container is a low-density polyethylene pre-filled syringe containing 8.4 g of product. Each syringe has an integrated adapter and with a "kg/body weight" graduation, in divisions of paste per 50 kg bodyweight.

Development pharmaceutics

Details of the optimisation of the formulation is provided along with information regarding the particle size of the active substance. Portions of active substance of different particle size were used. The ratio of micronised and unmicronised meloxicam used in the formulation was optimized based on the pre-clinical trials and the particle size specifications applied to the active substance reflect those for which suitable pharmacokinetics were obtained. The level of preservative in the formulation has been demonstrated to be effective with respect to antimicrobial preservation down to 70% of the nominal value in accordance with the shelf life specification for the preservative.

Method of manufacture

The manufacturing process is a standard one and consists of sequential addition of the excipients and active substance into a portion of purified water with mixing between additions. Adequate process validation data are provided with the application and full scale validation is to be completed post authorisation.

Control of starting materials

Active substance

The Active Substance Master File (ASMF) has been assessed in connection with previous Loxicom applications. A 24 month re-test period for meloxicam was accepted during previous authorisation procedure for Loxicom and is therefore acceptable for unmilled material. A 12 month re-test period for micronised meloxicam is acceptable based on the data presented in this application.

Excipients

All excipients except the apple flavouring material comply with their current European Pharmacopoeia (Ph. Eur.) monograph with additional functionality related limits for some excipients. Details of the qualitative composition of the apple flavour and an acceptable specification have been provided. Confirmation that the flavour meets food grade criteria has also been provided.

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

A TSE declaration for the product is provided confirming that all substances are sourced from non-animal origin and do not 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

The specifications proposed at release and shelf-life are appropriate to control the quality of the finished product. Test methods for identification and quantitative determination of meloxicam and related substances are described and are accompanied by validation data. Validation of the method for determination of the preservative content is also provided. Satisfactory batch analytical data has been provided.

Stability

Primary stability studies have been conducted on two production scale batches and on one laboratory scale batch. The real time storage conditions selected by the applicant are 30 ºC/65% RH rather than at 25 ºC/60% RH. Data at 6, 9, 12 and 18 months is available at 30 ºC/65% RH and 6 month data at 40 ºC/60% RH for all 3 batches. Out-of-specification results for benzyl alcohol and pH at 40 ºC/60% RH and decreases in the preservative content and pH at 30 ºC/65% RH mean that extrapolation of shelf life beyond that for which real time data is available is not possible. The applicant will submit the results of an on-going in-use stability study on a batch of product approaching the end of its shelf-life immediately upon its completion.

The following shelf life and storage precautions are supported by the data presented:

Shelf life of the veterinary medicinal product as packaged for sale: 18 months.
Shelf life after first opening the immediate packaging: 28 days
Store below 30 ºC.

Overall conclusions on quality

Details of the optimisation of the formulation regarding the choice of excipients and the particle size of the active substance were provided. The ratio of micronised and unmicronised meloxicam used in the formulation was optimized based on the pre-clinical trials. A 24 month re-test period for meloxicam was accepted for previous applications which is appropriate for unmilled material. A 12 month re-test period for micronised meloxicam is considered acceptable based on the data presented in this application.

All excipients comply with their Ph. Eur. monographs apart from the apple flavour for which an appropriate specification has been provided.

The manufacturing process is a standard one and adequate process validation is provided for authorisation. The specifications proposed at release and shelf-life are generally considered appropriate to control the quality of the finished product. Analytical methods have been satisfactorily validated. Full scale validation is to be completed post authorisation.

The following shelf life and storage precautions are supported by the data presented:

Shelf life of the veterinary medicinal product as packaged for sale: 18 months.

Shelf life after first opening the immediate packaging: 28 days

Store below 30 ºC.

Part 3 – Safety

This application has been made in accordance with Article 13(3) of Directive 2001/82/EC, as amended (a hybrid application). The reference product cited by the applicant that has been authorised within the EU is Metacam 15 mg/ml oral suspension for horses.

The concentration of the active substance meloxicam is higher in the proposed formulation of Loxicom 50 mg/g oral paste for horses when compared with the reference product Metacam 15 mg/ml oral suspension for horses.

Safety documentation

Pharmacodynamics

The pharmacodynamics properties of meloxicam have been characterised in the assessment of the reference product. In addition a brief overview was provided, together with a number of references, of the pharmacodynamic properties of meloxicam and other NSAIDs. Meloxicam is a member of the enolic acid class (oxicam sub-group) of non-steroidal anti-inflammatory drugs (NSAIDs) and is a non-chiral molecule. Meloxicam acts by inhibition of prostaglandin synthesis and thereby possesses analgesic, anti-inflammatory, anti-endotoxic, anti-exudative and antipyretic properties. The mode of action of meloxicam is *via* inhibition of cyclo-oxygenase (COX).

Pharmacokinetics

See Part 4.

Toxicological studies

A review of the peer-reviewed published literature on toxicity of meloxicam was provided, including information taken from the EMEA/CVMP MRL Summary Report for that substance summarised below.

Single dose toxicity: The acute oral toxicity has been investigated in rats, minipigs, mice and rabbits. The lowest oral LD50 of 83.5 mg/kg bw (males and females together) was determined in Chbb: THOM rats.

Repeat dose toxicity: Following oral repeat-dose administration to Wistar rats for 52 weeks, the oral No Observed Effect Level (NOEL) was established as 0.2 mg/kg bw. The same NOEL was determined following intravenous treatment for four weeks in Chbb: THOM rats. From an oral 13 week and 52 week study in minipigs, a NOEL of 1 mg/kg bw was derived. In dogs a NOEL of 0.4 mg/kg was determined in a 4-week study repeat dose oral study. However, in a 3-week repeat dose oral study, occult blood was observed even in the lowest dose (0.4 mg/kg bw) and a NOEL could not be determined. The target organs for toxicity are the gastrointestinal tract and the kidney.

Tolerance in the target species of animal: Tolerance in the target species is covered in Part 4 of this report.

Reproductive toxicity: Fertility indices were not affected by meloxicam. In a peri-postnatal study in Sprague Dawley rats a marginal prolongation of gestational length was observed at the lowest dose (0.125 mg/kg bw). This effect was considered to be of no biological importance. In teratogenicity studies in Chbb: THOM rats and rabbits NOELs for maternotoxicity were established as 1 and 20 mg/kg bw, respectively. There was no evidence for teratogenicity activity. However, meloxicam showed embryotoxic effects at the lowest doses tested (1 mg/kg) in these species.

Mutagenicity/genotoxicity: meloxicam was tested in a standard battery of genotoxicity tests and concluded not to be genotoxic.

Carcinogenicity: No evidence for carcinogenic activity was found in two-year dietary studies in mice and rats with doses of 2, 4 and 8 mg/kg bw daily and 0.4, 0.6 and 0.8 mg/kg bw daily, respectively.

The CVMP regarded the marginal effect on gestation length in the peri-postnatal reproductive toxicity study in Sprague Dawley rats as the most sensitive endpoint. Based on this study, the CVMP established a LOEL of 0.125 mg/kg. The effect observed at this dose is considered to be of no biological importance and consequently a safety factor of 100 was used to establish an ADI of 1.25 µg/kg bw.

Studies of other effects

Special studies

Information on special studies is reported in derived from the EMA/CVMP MRL summary report for meloxicam and/or the EPAR for the reference product, Metacam.

The available data indicate that the active substance is not a dermal/ocular irritant, does not have sensitisation potential and is absorbed to a limited extent following skin contact. Meloxicam is used in human medicine for the treatment of rheumatoid arthritis and osteoarthritis. Daily oral doses of 7.5 mg or 15 mg per person are recommended, corresponding to approximately 0.125 or 0.25 mg/kg bw per day.

Local effect studies with the final formulation were not conducted.

User safety

A user safety assessment was provided.

The product is presented in a ready-to-use form and therefore risk of exposure during pre-application is minimal. However, there may be a risk of dermal, oral or ocular exposure during the application phase. A quantitative risk assessment following exposure via the oral, dermal and ocular routes was provided.

Based on the assessment conducted, a potential risk associated with oral exposure was identified. This potential risk is adequately mitigated by inclusion of the following wording in section 4.5 of the SPC:

'*In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.*'

Information on local effects for the final formulation was not provided. While it is noted that the active substance is not recognised as a dermal/ocular irritant or a skin sensitiser, a number of the excipients have the potential to cause skin and/or ocular irritation (in particular, benzyl alcohol) and skin sensitisation (benzyl alcohol). This potential risk is adequately mitigated by inclusion of the following wording in section 4.5 of the SPC:

'Avoid skin and eye contact with the product. If skin and/or eye contact occurs, wash the affected parts immediately with water. Should irritation occur and persist, seek medical advice'.

In addition, in line with text agreed for products of this class, the following wording is included in section 4.5:

'*People with known hypersensitivity to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should avoid contact with the veterinary medicinal product.*'

Noting the user safety statements proposed for inclusion on the product literature, CVMP concluded that the product, when used in accordance with label recommendations, will not pose an unacceptable risk to the user.

It was demonstrated that the immediate packaging is child-resistant and therefore the risk of accidental ingestion by a child is considered low for this product.

Environmental risk assessment

The applicant has provided an environmental impact assessment in accordance with the Guideline on Environmental Impact Assessment for Veterinary Medicinal Products – Phase I (CVMP/VICH/592/98-FINAL) by following the phase I decision tree included in the relevant guidelines.

For the purposes of the ERA, the horse is considered a minor species. In addition, it can be accepted that the product will be used to treat a small number of animals on a premises or individual horses. As such, it can be accepted that the ERA conclude at Phase I. A Phase II environmental impact assessment is not required.

It can be concluded that the product will not pose an unacceptable risk for the environment when used in accordance with the recommendations included in the SPC.

Overall conclusions on the safety documentation

This application has been made in accordance with Article 13(3) of Directive 2001/82/EC, as amended (a hybrid application) with Metacam 15 mg/ml oral suspension as reference product. The concentration of the active substance meloxicam is higher in the proposed formulation of Loxicom 50 mg/g oral paste for horses when compared with the reference product.

An extensive review of the published literature has been provided in order to address the pharmacological and toxicological aspects of the active substance. Additionally, reference was made to the MRL summary report for meloxicam. Based on the data presented, the pharmacological and toxicological profile of the active substance has been adequately characterised.

In support of the application, target animal safety studies were provided as described in part 4 of this report.

The applicant provided a user risk assessment. Based on the assessment presented, CVMP concluded that the product, when used in accordance with label recommendations, will not pose an unacceptable risk to the user. It was demonstrated that the immediate packaging is child-resistant and therefore the risk of accidental ingestion by a child is considered low for this product.

It can be concluded that the product will not pose an unacceptable risk for the environment when used in accordance with the recommendations included in the proposed SPC.

Residues documentation

Identification of the product concerned

The formulation of the product includes the active substance meloxicam and the excipients hydroxypropyl cellulose, glycerol, xanthan gum, sorbitol, benzyl alcohol, saccharin sodium powder, apple flavour and purified water.

Pharmacokinetics

See Part 4.

Depletion of residues

A residue depletion study was provided in the target species following administration of Loxicom 50 mg/g oral paste.

This was a GLP compliant study including four animals sacrificed at one time point (3 days which is the withdrawal period approved for the reference product). The number of animals included in the study is less than the number recommended for single time point studies in VICH GL 48 on marker residue depletion studies to establish withdrawal periods. However, as the study was conducted before the VICH guideline came into effect (February 2012) and as the number of animals used is consistent with the guidance in force at the time the study was performed the study can be accepted. The animals included in the study were accepted as being representative of the intended target population.

The target dose of 0.6 mg/kg bw meloxicam was administered once daily for 14 consecutive days per os. The product was administered over the tongue with the animal's head being kept raised until the product was swallowed. Animals were sacrificed 3 days after the final administered dose and muscle, liver, kidney and fat samples were harvested.

Levels of Meloxicam above the Limit of Quantification (10 µg/kg) were not detected in any tissue sample at the 3 day slaughter time point. The applicant has determined that residue concentrations of meloxicam are less than the MRLs for muscle (20 µg/kg), liver and kidney (both 65 µg/kg) 3 days after final administration of the product.

Pharmacokinetics

See Part 4.

MRLs

The active substance in Loxicom is meloxicam, 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 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 not to fall within the scope of Regulation (EU) No 470/2009 when used as in this product.

Withdrawal periods

The provided single timepoint residue depletion study as described above was designed to provide confirmation that the MRLs would not be exceeded at the proposed withdrawal period. Given the nature of the application (generic), the study can be accepted as a confirmatory study.

Based upon the results of the residue depletion study conducted where all meloxicam concentrations were found to be below the Limit of Quantification (10 µg/kg) in all tissues analysed three days after the final administration of the product), it can be concluded that residues of meloxicam deplete at a rate that is at least as fast as that observed for the reference product. The same withdrawal period approved for the reference product (3 days) is therefore applicable for Loxicom oral paste. The following text is proposed for inclusion in section 4.11 of the SPC:

Meat and offal: 3 days.

Not authorised for use in animals producing milk for human consumption.

Analytical methods

An acceptable method validation report has been provided in support of the method used in determining Meloxicam concentrations in equine tissues.

Overall conclusions on the residues documentation

A single time point residue depletion study has been conducted in order to demonstrate that the withdrawal period approved for the reference product (3 days) is also appropriate for Loxicom 50 mg/g oral paste. A withdrawal period of 3 days for meat and offal is established. The product is not authorised for use in animals producing milk for human consumption.

Part 4 – Efficacy

Pharmacokinetics

The applicant has conducted an extensive review of the published literature in order to characterise the specific pharmacokinetic properties of meloxicam and with particular reference to horses.

In addition, the applicant conducted a GLP compliant in vivo bioavailability study ,in accordance with Guideline on the conduct of bioequivalence studies for veterinary medicinal products - EMA/CVMP/016/00-Rev.2, in order to compare the plasma concentration profile of meloxicam between the product Loxicom 50 mg/g oral paste and the reference product containing meloxicam (Metacam) 15 mg/ml oral suspension for horses. Sixteen horses were included in a cross-over design study with two treatment periods (I and II) and a wash out period of 6 days between treatment periods. Horses were male, aged 4 to 5 years and in the weight range of 379 to 550 kg within 1 day prior to first administration. Animals were randomly assigned to one of two groups (8 animals in each group) using a blocking system following ordering by weight in order to minimise weight differences between groups.

Following weighing, and rounding up to the nearest 50 kg, all animals were administered the product/reference product at a dose rate of 0.6 mg meloxicam/kg bw (based upon nominal meloxicam concentrations) on a single occasion during each period of the study. The dose was administered into the mouth over the tongue and the animal's head was kept raised until the product was swallowed.

Blood samples for plasma meloxicam determination were collected from the jugular vein on a number of occasions in each period of the study. The plasma concentrations of meloxicam were determined using a validated HPLC assay method and used to determine the pivotal pharmacokinetic parameters C_{max} and AUC. The results of the comparative bioavailability study confirm that bioequivalence has been demonstrated for AUC only, but not for C_{max}. The 90% confidence intervals for the estimate of the ratio of the means for the parameter AUC are within the narrower limits of 80% to 125%. However, for C_{max}, the upper limit of the wider limits for the 90% confidence interval (1.43) has been exceeded. No adverse events were observed in this study.

Based on the AUC data, the CVMP concluded that systemic availability is sufficiently similar for both product and reference product, and it is expected that both will behave similarly from the point of view of efficacy.

However, given that bioequivalence in terms of C_{max} was not demonstrated concerns in respect to the safety of the product were raised (safety for the consumer and safety for the target animal). In order to address these concerns, the applicant conducted a confirmatory residue study (see Part 3) and two target animal safety studies supported by a an additional field safety study (see below).

Pharmacodynamics

See Part 3.

Target Animal Tolerance

In support of the safety of the product in the target species, the applicant conducted two target animal tolerance studies, a confirmatory residue depletion study and during the course of the application procedure presented the results of another study – a field safety study.

The first study was conducted in 15 male horses randomised into three groups of five animals. Animals were either administered the product at the recommended treatment dose (RTD), at 3xRTD or a placebo formulation without the active substance once daily for a period of fifteen days. Clinical observations were performed daily throughout the study. Blood samples were collected for biochemical and haematological analysis at specified time points during the study. Bodyweights were monitored and faecal analysis for occult blood was performed.

There were deficiencies in the study design relative to the recommendations in the relevant guideline (VICH Topic GL43 EMEA/CVMP/VICH/393388/2006): the product was administered at 3x the RTD and not 5x the RTD for a period of time that did not exceed three times the proposed treatment duration and evaluated a single gender only with limited numbers of horses. Notwithstanding these deficiencies, the results of this study indicated that the product had an acceptable tolerance profile in the target species when administered at doses of up to three times the recommended treatment dose for a period of up to fifteen days (one day in excess of the proposed treatment duration).

In the second target animal tolerance study, 12 male horses were randomised into three groups of four animals. Animals were to be either administered the product at the recommended dose rate, at 5xRTD or a placebo formulation without the active substance once daily for a period of fifteen days.

Clinical observations were performed daily throughout the study. Blood samples were collected for biochemical and haematological analysis at specified time points during the study. Bodyweights were monitored and faecal analysis for occult blood was performed.

The findings of this study show that the product was not well tolerated in the target animal at a dose rate of 5xRTD (3 mg/kg). Administration had to be discontinued after only 7 consecutive days of treatment (only half of the proposed treatment duration of 14 days).

Like the rpevious tolerance study, there were deficiencies in the study design relative to guideline recommendations: the product was administered at 5xRTD for a period of time that did not exceed three times the proposed treatment duration and evaluated a single gender only with limited numbers of horses. Notwithstanding these deficiencies, it is accepted that both target animal safety studies indicated that no tolerance issues of concern occurred in animals administered the product at the recommended treatment dose of 0.6 mg/kg (1xRTD) or doses up to 3xRTD, but all animals in the 5xRTD group experienced adverse reactions, and the safety margin for the product appeared to be relatively narrow.

Given the severity of findings when the product was administered at the 5x overdose, and the deficiencies noted in the study design of the two studies, further data were requested by the CVMP (new field study - see below).

Dose determination / justification

No data were provided. The proposed posology (0.6 mg/kg) for up to 14 days was justified as it is the same as for the reference product.

Dose confirmation

No data were provided asthe proposed dose rate of 0.6 mg/kg is the same as for the reference product.

Field safety study

A well conducted multi-centrered, controlled GCP compliant field safety study was presented during the course of the application procedure in response to the CVMP List of Questions. This study investiged the tolerance of 45 horses following oral administration at the recommended therapeutic dose (0.6 mg meloxicam/kg bodyweight) of the product once daily for 14 days, compared with controls. The study was conducted at three sites (farms) including animals representative of the intended target population in terms of breed, age, gender and weight. Throughout the study the animals were group monitored at each farm for any observable illness or injury. In addition, faecal samples were taken from each animal during selection and at the end of the animal phase. The range of biochemical and haematology parameters measured in this study was somewhat limited but chosen based on relevance for possible signs of toxicity to meloxicam.

The results of the field safety study indicated that

- None of the key parameters demonstrated a significant difference between both the test group and control animals.
- Product administration had to be stopped in two out of 45 animals due to the onset of gastrointestinal signs (diarrhoea). The possibility that the adverse events recorded for these two animals were treatment-related cannot be excluded. It is noted that the section 4.6 of the proposed SPC includes a statement advising of the potential for diarrhoea to occur as an adverse effect of treatment.
- Hypoalbuminaemia was observed only in animals administered the test product and this occurred in aproximately 24% of animals. Similar findings in respect of hypoalbuminaemia were also noted in the two target animal safety studies.

The results of this study, in addition to the two target animal safety studies, were considered sufficient to conclude on an acceptable target animal tolerance for the product. However, adverse reactions

might occur at the recommended treatment dose, and this effect increases in a dose dependent manner. Therefore, adequate warnings were added to the SPC and product literature.

Overall conclusion on efficacy

The applicant has provided the results of a bioavailability study designed to compare the pharmacokinetic profiles of meloxicam in equine plasma between the product Loxicom 50 mg/g oral paste and the reference product containig meloxicam at 15 mg/ml oral suspension, as described above. Based on the results bioequivalence between test and reference product can be accepted for the parameter AUC but not for the parameter $C_{max.}$

From this, it can be concluded that systemic availability is sufficiently similar for both products that they will behave similarly from the point of view of efficacy.

Given that bioequivalence in terms of C_{max} has not been demonstrated, target animal tolerance could be extrapolated from the reference product, and additional target animal safety data were considered necessary.

In support of the application , two target animal safety studies were conducted using the test product, Loxicom 50 mg/g oral paste. In these studies, tolerance of the product was acceptable at a dose up to 3xRTD. The results of the target animal tolerance studies suggest that the product is poorly tolerated when administered at 5xRTD. However, the studies provided are somewhat limited and deviate from guideline requirements (in terms of animal numbers and design). These two studies were therefore not considered sufficient to provide adequate assurances on the safety of this specific formulation.

In response to these concerns, the applicant presented the results of an additional field safety study in which 45 animals were administered the Loxicom 50 mg/g oral paste at the recommended treatment dose (0.6 mg meloxicam/kg bodyweight) under field conditions of use. Based upon the findings from this additional study and the two previous tolerance studies, it was concluded that a narrow safety margin in terms of treatment dose exists for this product. It is evident that a reduction in blood albumin concentration commonly occurs at the recommended treatment dose and that this effect increases in a dose dependent manner. In addition, based upon the data presented, the possibility for diarrhoea to occur in some animals following administration of the product cannot be excluded.

Appropriate additional warnings were therefore included in the SPC and product literature.

Part 5 – Benefit risk assessment

Introduction

Loxicom 50 mg/g oral paste for horses is an extension application for a new pharmaceutical form and presented as a generic (hybrid) product application. It includes meloxicam as active substance.

The chosen reference product also contains 15 mg meloxicam/ml as oral suspension for horses. Loxicom is already authorised for use in horses as an injectable formulation to relieve colic (abdominal pain) and the inflammation and pain in musculoskeletal disorders.

The product is intended to be presented in 8.4 g dial-a-dose syringes and will be administered directly into the mouth of the horse.

The product is indicated for the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses.

Benefit assessment

Direct therapeutic benefit

The active substance is a well-known NSAID. Meloxicam acts by inhibition of prostaglandin synthesis and thereby possesses analgesic, anti-inflammatory, anti-endotoxic, anti-exudative and antipyretic properties. The mode of action of meloxicam is via inhibition of cyclo-oxygenase (COX).

Direct therapeutic benefits are the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses. This is considered to result from the anti-inflammatory effect of meloxicam and especially in terms of the published data which would suggest that Meloxicam is preferentially a selective inhibitor of the COX-2 isoform of cyclo-oxygenase.

Additional benefits

The availability of a new pharmcaceutical form (oral paste that can be administered by the horse owner) will increase the range of available treatment possibilities and may in some circumstances negate the need for administration of injectable preparations thus avoiding the risks associated with parenteral administration.

Risk assessment

Loxicom 50 mg/g oral paste for horses is expected to have the same risks as the reference product. However, the following additional risks were identified.

The product has a narrow safety profile. Whilst tolerance has been shown at the recommended dose, serious reactions have been observed at overdose of 5xRTD.

Based on the user risk assessment conducted, a potential risk associated with oral exposure was identified as well as a potential risk posed by some excipients due to their potential to cause skin and/or ocular irritation and skin sensitisation.These potential risks are adequately mitigated by inclusion of appropriate wordings in the SPC. The potential risk of accidental intake by a child is considered low as the immediate packaging can be considered as being child-resistant.

The product is not expected to pose a risk for the environment when used as recommended.

Risk management or mitigation measures

Appropriate advice, as for the authorised reference product, is included in the SPC and product information to prevent risks for the target animal, the user and for the environment.

Additional warnings are included in the SPC and package leaflet to mitigate the risk to the user after accidental oral/dermal/ocular exposure and to prevent a risk to the target animal in case of an overdose.

It is accepted that the withdrawal period for meat in horses is the same as the one established for the reference product (meat: 3 days). The product is not authorised for use in animals producing milk for human consumption.

Evaluation of the benefit risk balance

The product has been shown to have a positive benefit-risk balance overall.

The formulation and manufacture of Loxicom 50 mg/g oral paste for horses is well described and specifications set will ensure that product of consistent quality will be produced.

As it was shown that the systemic bioavailabity of Loxicom 50 mg/g oral paste for hores will be the same as that for the reference product it can be concluded that Loxicom 50 mg/g oral paste for horses will be as efficacious as the reference product for the indications as stated in the SPC.

It was shown that a narrow safety margin in terms of treatment dose exists for Loxicom 50 mg/g oral paste in horses and risks were identified at overdose. To ensure the safety for the target animals appropriate information and warnings are included in the SPC.

Additional warnings to those of the reference product in the SPC are included in order to mitigate any unacceptable risk for the user after oral, dermal or ocular exposure.

The withdrawal periods for meat/offal are the same as for Metacam 15 mg/ml oral suspension for horses. Loxicom presents a low risk to the environment when used as recommended and appropriate advice has been included in the SPC.

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 Loxicom 50 mg/g oral paste for 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.