7 September 2023
EMA/426856/2023
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Loxitab (EMEA/V/C/006099/0000)

INN: meloxicam

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

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Introduction

The applicant CP-Pharma Handelsgesellschaft mbH submitted on 22 July 2022 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Loxitab, through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (optional scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 16 March 2022 as no other marketing authorisation has been granted for the veterinary medicinal product within the Union.

At the time of submission, the applicant applied for the following indication:

Alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders in dogs.

The active substance of Loxitab is meloxicam, a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class which acts by inhibition of prostaglandin synthesis, thereby exerting anti-inflammatory, analgesic, anti-exudative and antipyretic effects. The target species is dogs.

Loxitab tablets contain 1 mg or 2.5 mg of meloxicam and are presented in packs containing 1 blister x 10 tablets, 3 blisters x 10 tablets, 5 blisters x 10 tablets and 10 blisters x 10 tablets.

The rapporteur appointed is Leona Nepejchalová and the co-rapporteur is Cristina Muñoz Madero.

The dossier has been submitted in line with the requirements for submissions under Article 19(1) - hybrid (change in strength) as the quantitative composition of the active substance in Loxitab is different to that in the reference product Metacam 1.5 mg/ml oral suspension for dogs. Metacam (EU/2/97/004) was first granted a Union marketing authorisation on 7 January 1998.

On 7 September 2023, the CVMP adopted an opinion and CVMP assessment report.

On 19 October 2023, the European Commission adopted a Commission Decision granting the marketing authorisation for Loxitab.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF), has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

The active substance, meloxicam, is manufactured by two different suppliers. The qualified person (QP) declaration for the all active substance manufacturing sites and all intermediates manufacturing sites was provided from the QP at the EU batch release site. The QP declaration states that the active substance is manufactured in compliance with EU GMP. The declaration is based on on-site audits of all manufacturing locations which were performed by third parties.

Finished product

Batch release is performed by:

CP-Pharma Handelsgesellschaft mbH
Ostlandring 13, 31286 Burgdorf, GERMANY

The Manufacturing Authorisation issued on 6 January 2022 is available in EudraGMDP.

A GMP certificate issued by the Competent Authority is available in EudraGMDP. The certificate was issued on 6 November 2020, referencing an inspection on 8 September 2020. EudraGMDP document reference number is 107706 (certificate number: DE_NI_02_GMP_2020_0046).

Manufacture, quality control testing (microbiological and chemical/physical), and primary and secondary packaging of the finished product take place at several places in the EEA. All sites involved have a manufacturing authorisation issued by the corresponding competent authority. GMP certification, which confirms the date of the last inspection and shows that the sites are authorised for the activities indicated above, are available in EduraGMDP.

For one of these sites the last inspection took place more than 3 years ago but in accordance with the Notice to stakeholders on Regulatory expectations for VMPs during the COVID-19 pandemic, the validity of the latest GMP certificate is automatically extended until the end of 2023 without the need for further action from the holder.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file was considered to be in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The product meloxicam tablets is a veterinary medicinal product containing 1 mg and 2.5 mg of meloxicam (Ph. Eur.) as the active substance. It is a light brown with brown spots, round and convex tablet with a cross-shaped break line on one side. Both tablet strengths have the same qualitative composition and they are quantitatively proportional: the 1 mg strength with 8 mm diameter, and the 2.5 mg strength with 12 mm diameter. The tablets are divisible into 4 equal parts (quadrisect) to improve dose accuracy.

Other ingredients are: lactose monohydrate, cellulose microcrystalline, sodium citrate, crospovidone, silica, colloidal hydrated, magnesium stearate, yeast dried and chicken flavour. Information regarding excipients is considered acceptable.

Containers and closure system

The product is packed in PVC/PE/PVDC (white)-Alu blisters, containing 10 tablets each. The pack sizes are 1, 3, 5 or 10 blisters in a cardboard box. The PVC foil complies with the Ph. Eur. 3.1.11 and Commission Regulation (EU) 10/2011 as amended. The aluminium foil complies with EU Regulations

1935/2004 and 2023/2006. Satisfactory specifications are provided for the blister foils. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Certificates of analysis for each material are provided and the results comply with the specification.

Bulk tablets are packed in double polyethylene (PE) bags (outer black). The PE complies with Commission Regulation (EU) 10/2011 as amended. Certificate of analysis is provided and the results comply with the specification.

Product development

The aim of the development was to obtain meloxicam 1 mg and 2.5 mg tablets bioequivalent to Metacam 1.5 mg/ml oral suspension for dogs (Boehringer Ingelheim Vetmedica GmbH, Germany). As the test product represents a different dosage form, its formulation cannot be directly based on the originator. The applicant therefore takes into account the excipients used in Metacam tablets. The choice of excipients is typical for tablets, the function of each excipient is shortly explained and accepted.

Solubility of meloxicam is pH dependant as it increases with the increase of pH. This characteristic of meloxicam is confirmed with the dissolution profiles provided by the applicant.

Development of the dissolution method is based on the requirements established in the CVMP Guideline on bioequivalence (EMA/CVMP/016/2000) and also on the Ph. Eur. 2.9.3 and 5.17.1. The finished product dissolution specification is in line with the requirements in the Reflection paper on dissolution specification for generic solid oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017).

Discriminatory power of the dissolution method is confirmed by testing biobatch vs. "bad-batch". The dissolution profile of the "bad-batch" is slow and the batch is not compliant with the finished product specification.

An in-vivo bioequivalence study is carried out with Loxitab 2.5 mg tablets and the originator Metacam 1.5 mg/ml oral suspension. The difference in assay of biobatches is within 5% between the test product and the originator as required in the CVMP guideline on bioequivalence studies. The bioequivalence of the 1 mg strength is shown by an in-vitro dissolution study. This approach is acceptable.

Comparative dissolution studies are carried out at three pH: 1.2, 4.5 and 7.5. In accordance with the guideline on bioequivalence, the company performed comparative dissolution profiles for process validation batches of the smallest commercial size proposed with satisfactory results and committed to perform comparative dissolution profile on the first three full-scale batches of maximum size.

The functionality of the tablet break line is confirmed by the Ph. Eur. test Subdivision of tablets as described in the general monograph "Tablets". The study is carried out on three process validation batches.

Based on the proposed manufacturing process (direct compression), further information is provided in regard to the particle size control for excipients. The applicant has demonstrated on a number of batches that the particle size control of the components together with the manufacturing process conditions are adequate to achieve the required tablet homogeneity and performance (process validation, uniformity of dosage units test).

Tablets are manufactured using multiple blending steps followed by tabletting (dry compacting) and packaging. The manufacture is a dry process.

Comparative data are given for three process validation batches of each strength vs. two batches of originator product (biobatches are included). Similarity is shown.

Description of the manufacturing method

A batch size range of powder blend is proposed. Both tablet strengths can be compressed out of one powder blend (proportional tablets). The number of tablets per batch are calculated for each strength.

The manufacturing is a straightforward process consisting of the preparation of the tablet mixture that is tabletted by dry compression and packed into blisters. The process is described in a stepwise manner including sufficient details on process conditions and in-process controls. The c bulk holding time proposed is supported by stability data (see below).

The manufacturing process is by default considered non-standard as it is a unit dose product containing the drug substance in low content (≤2% of composition, Annex II to the guideline on process validation of finished products EMA/CHMP/CVMP/QWP/BWP/70278/2012). Three production scale batches of the smallest size are validated with both strengths. The process validation results demonstrate homogeneity of the batches and consistency of the process. The validation data submitted demonstrate that a reproducible product quality within the specified limits is achieved using the manufacturing process described.

A holding time study is carried out with two batches of the bulk tablets (two powder blends compressed into both tablet strengths) stored in double PE bag, inner transparent and outer black, and with a desiccant placed between both bags. Samples for the study are tested on appearance, uniformity of mass, disintegration time, friability, resistance to crushing, water content, assay and identification, dissolution, related substances, microbiological purity and subdivision of tablets (halves and quarters). All results comply with the quality requirements, no degradation is observed.

The process validation study is satisfactory for the smallest batch size. The company provides additional justification to consider their process as standard taking into account the manufacturer's experience with similar products. Information is provided regarding similarity of the manufacturing processes and the number of batches already manufactured. On the basis of the company's justification, the process can be considered standard for the manufacturer and the maximum batch size proposed with the validation commitment is acceptable.

Control of starting materials

Active substance

The active substance meloxicam is controlled as per the Ph. Eur. monograph 2373.

Two manufacturers are proposed by the applicant, one with an ASMF and one with a CEP. Both sources list as additional test a control of residual solvents. The applicant's own specification reflects these additional controls accordingly. The limits are compliant with the VICH GL18/Ph. Eur. 5.4. and the control methods are referred to the ASMF or the CEP as relevant.

Control of particle size is included in the active substance specification and the control methods (laser diffraction) are suitably described and validated by the active substance manufacturers.

Meloxicam shows polymorphism and according to the analytical data provided by both manufacturers, the same polymorphic form is consistently produced. Control of the polymorphic form is anyhow

introduced in the applicant's active substance specification as non-routine test in case of future change in the manufacturer of meloxicam.

The ASMF provided by one of the manufacturers is acceptable.

Certificates of analysis are provided for three commercial batches manufactured by both sources of meloxicam (ASMF and CEP holders). The applicant has provided also their own batch data demonstrating consistency with the data by ASMF/CEP holders and compliance with established specification.

In regard to retest periods, the applicant refers to the ASMF and CEP where the data were assessed and accepted. For both manufacturers, a retest period of 5 years is accepted without any special storage recommendations.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. except for the flavouring agents. The excipients chicken flavour and yeast (dried) are controlled in line with in-house specifications. Satisfactory specifications in line with the current Guideline on excipients for veterinary medicinal products (EMA/CVMP/QWP/307647/2023) are provided for both flavouring agents, including control of microbiological quality. A viral safety evaluation in accordance with Ph. Eur. was submitted for the chicken flavour. There are no novel excipients used in the finished product formulation.

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

Both manufacturers of meloxicam declare that they do not use any material of human or animal origin during the manufacture of the active substance.

The finished product contains lactose and chicken flavour, which are both of animal origin. It is confirmed by the supplier of the magnesium stearate that the source is 100% non-animal origin. Appropriate declarations are provided for the excipients.

No TSE risk or viral safety risk are identified.

Control tests on the finished product

The finished product specification is established following the requirements of Regulation 2019 (EU) 2019/6, Ph. Eur. general monograph 0478 on Tablets and VICH GL39.

The finished product release specification includes tests for appearance (visual), tightness of blister (blue bath test), average mass (weight), uniformity of dosage units (Ph. Eur., by CU), identification of meloxicam (HPLC and UV), assay (HPLC), impurities (HPLC, non-routine test), dissolution (Ph. Eur.) and microbiological purity (Ph. Eur., non-routine test).

The analytical methods used have been described and validated in accordance with the VICH guidelines.

Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis results are provided for three powder blend batches compressed into both strengths confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Risk assessment of potential elemental impurities is provided following the principles established in the ICH Q3D. The company follows the component approach and compliance with control strategy option 2b is shown. No risk is identified.

Stability

Stability data were provided for three powder blend batches (commercial scale smallest size) which were compressed into both strengths 1 mg and 2.5 mg tablets of the finished product. These are the same batches as used for process validation and batch analysis.

The tablets are stored under long term conditions at 25 ºC/60% RH with results available for 24 months (plan up to 36 months) and under accelerated conditions for up to 6 months at 40 ºC/75% RH according to the VICH GL3 on stability testing of new veterinary drug substances and medicinal products. The product batches are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

The differences between the release and shelf-life specification have been adequately justified.

The long-term stability data does not indicate any significant degradation. Acceptable impurities increase is observed. Some variability of results for assay can also be observed but this could be attributed to the analytical method and sampling variability rather than degradation. Some water uptake is also observed

In addition, one batch was checked on photostability. The study follows principles established in the VICH GL5. The results under all conditions remained similar and thus showed that the product is not sensitive to light.

In-use stability was also tested on one batch (tablet broken into 4 quarters) and it showed that the product is stable when outside of the packaging for three days.

Considering satisfactory accelerated data and on long-term studies without significant changes up to 24 months, the shelf-life can be extrapolated up to 36 months as claimed by the company. A commitment has been provided as per the stability guideline EMA/CVMP/QWP/709423/2022, section 2.2.8 (point 1) as the long-term stability studies are still on-going.

The proposed storage conditions as stated in the SPC are accepted (no special storage conditions are needed).

Overall conclusions on quality

Loxitab tablets contain 1 mg or 2.5 mg of meloxicam and are manufactured by direct compression of the powder blend which is composed of meloxicam as active substance and the following excipients: lactose monohydrate, cellulose microcrystalline, sodium citrate, crospovidone, silica colloidal hydrated, magnesium stearate, yeast dried and chicken flavour.

The aim of the product development was to obtain meloxicam 1 mg and 2.5 mg tablets bioequivalent to Metacam 1.5 mg/ml oral suspension for dogs. As the test product represents a different dosage form, the excipients used in Metacam tablets are the basis for the choice of excipients in Loxitab.

An in-vivo bioequivalence study demonstrated bioequivalence between Loxitab 2.5 mg tablets and the originator Metacam 1.5 mg/ml oral suspension. The bioequivalence of the 1 mg strength is shown by an in-vitro dissolution study.

Development of the dissolution method is based on the requirements established in the CVMP Guideline on bioequivalence and Ph. Eur. The discriminatory power of the dissolution method has been demonstrated.

The manufacturing process is described in sufficient detail and appropriate IPCs are in place. It is considered by default a non-standard process since the amount of active substance is ≤2% of the composition. The process has been adequately validated in three commercial scale batches (smallest size proposed) of the powder blend which is afterwards used to manufacture both tablet strengths. The applicant has adequately demonstrated that the process can be considered standard for the proposed manufacturer of commercial batches and therefore the commercial batch size range proposed can be accepted.

Two suppliers of active substance have been proposed, one with an ASMF and one with a CEP.

The specification for the active substance applied by the dosage form manufacturer is acceptable as well as the analytical methods. Acceptable certificates of analysis have been provided by both suppliers of active substance as well as from the dosage form manufacturer.

For both manufacturers, a retest period of 5 years is accepted without any special storage recommendations.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. except for the flavouring agents which are controlled in line with in-house specifications.

No TSE risk or viral safety risk are identified for the excipients or the active substance.

Acceptable specification have been set for the finished product at release. Batch analysis results provided confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification. No risk is identified in terms of control of elemental impurities.

The differences between the specification at release and at shelf-life have been adequately justified.

Stability data from 3 powder blend production scale batches and compressed into both tablet strengths were provided (6 months at accelerated conditions and 24 months at long term conditions). Photostability data provided on one batch and on in-use stability was also provided. Results are satisfactory and a shelf-life of 36 months (by extrapolation) without any special storage conditions is accepted.

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

In regard to the ASMF, no questions are raised and the ASMF is acceptable.

Part 3 – Safety documentation

The dossier has been submitted in line with the requirements for submissions under Article 19(1) - hybrid (change in strength).

The active substance of Loxitab 1 mg and 2.5 mg tablets for dogs is meloxicam, a non-steroidal anti-inflammatory drug (NSAID). Loxitab contain 1 mg or 2.5 mg of meloxicam per tablet. The target species is dogs.

The reference product is Metacam 1.5 mg/ml oral suspension for dogs (EU/2/97/004). Metacam was first granted a marketing authorisation following a centralised procedure on 7 January 1998.

Safety tests

As bioequivalence with the reference product has been demonstrated, and considering the legal basis of the application, data from pharmacological and toxicological studies are not required and can be assumed from the reference product. A user risk assessment (URA) and environmental risk assessment (ERA) have been provided.

Meloxicam was previously assessed by the CVMP and a toxicological ADI of 1.25 µg/kg bw (equivalent to 75 µg for a 60 kg person) was established. The safety evaluation carried out by the CVMP is reported in detail in the MRL summary report (EMEA/MRL/571/99-FINAL).

Pharmacology

See part 4.

Excipients

The excipients lactose monohydrate, microcrystalline cellulose, sodium citrate, crospovidone, colloidal hydrated silica, and magnesium stearate are widely used in oral pharmaceutical products intended for use in humans and they are therefore not considered to present a safety concern. Natural chicken flavour and dried yeast are also considered safe.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with the CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1). The composition in excipients of the candidate product differs from that of the reference product and information on the user safety of the excipients has been provided. The main potential routes of accidental contact with the product have been considered and it was concluded that the most likely are those of direct dermal exposure for non-professional user and accidental ingestion by a child, that could be considered as the worst-case scenario. The LOEL of 0.125 mg/kg bw, based on prolonged gestational length in reproductive toxicity study in rats, was used for establishment of toxicological ADI for meloxicam. Treatment of a 50 kg dog using 0.1 mg/kg bw and exposure to 1% of this amount were used for the quantitative risk calculation for the non-professional user. A margin of exposure (MOE) of 150 has been calculated. Therefore, a risk for the adult user is not expected.

The exposure to 1 tablet with 2.5 mg of meloxicam was used for the calculation of the risk of accidental ingestion by a 10 kg child and comparing to the dosage in human medicinal products the exposure is assessed to be 1 to 2 times higher than the therapeutical dose and the LOEL value used for toxicological ADI establishment. A risk for children is therefore identified. Appropriate warnings have been included in the product information in order to mitigate this risk. A standard warning relating to hypersensitivity to NSAIDs is also included.

Based on the above risk assessment the CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC. User safety warnings are adequately described in section 3.5 of the SPC.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the relevant CVMP/VICH guidelines (i.e., VICH GL6 and the CVMP 'Guideline on the environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38' [EMEA/CVMP/ERA/418282/2005-Rev.1]).

It was concluded that the assessment can stop in Phase I, and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food producing species (dogs).

As is the case for the reference product, no specific environmental warnings are considered necessary and the standard text relating to disposal of unused product is proposed for inclusion in the SPC of Loxitab 1 mg and Loxitab 2.5 mg tablets for dogs.

It can be concluded that this product will not present an unacceptable risk for the environment when handled, used, stored and disposed of in accordance with the recommendations included in the proposed SPC.

Overall conclusions on the safety documentation

Pharmacology:

See part 4.

Toxicology:

The CVMP Summary report on meloxicam (EMA/MRL/571/99-FINAL) has been submitted. The safety evaluation carried out by the CVMP is reported in detail in the MRL summary report (EMEA/MRL/571/99-FINAL).

The LOEL 0.125 mg/kg bw, based on prolonged gestational length in reproductive toxicity study in rats, was used for establishment of toxicological ADI for meloxicam. The data presented are considered adequate to characterise the toxicity profile of the active substance.

User safety:

A user safety assessment in line with the relevant guidance document has been presented. Since the composition in excipients of the candidate product differs from that of the reference product, the applicant provided a brief comment on the safety of the excipients to confirm they do not present a safety concern.

Based on the assessment provided, the potential health risk of the product to adult users is considered low and acceptable when used in accordance with the SPC. The worst-case scenario for user safety is an accidental ingestion of 1 tablet by a child. Appropriate warnings have been included in the product information in order to mitigate this risk. The CVMP concluded that the products Loxitab 1 mg and Loxitab 2.5 mg tablets for dogs are not expected to pose a risk to the user when used in accordance with the SPC.

Environmental risk assessment:

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

It was concluded that the assessment can stop in Phase I, and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food producing species (dogs).

The products Loxitab 1 mg and Loxitab 2.5 mg tablets for dogs are not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Pre-clinical studies

Loxitab tablets contain meloxicam, a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class intended for use in dogs for alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders. The proposed dose is a single dose of 0.2 mg meloxicam/kg body weight on the first day followed by a maintenance dose of 0.1 mg meloxicam/kg body weight once daily.

Pharmacology

Pharmacodynamics

This is a hybrid application and the applicant has claimed bioequivalence with the reference product Metacam 1.5 mg/mL oral suspension for dogs (Boehringer Ingelheim Vetmedica GmbH). Meloxicam is an NSAID acting by inhibition of prostaglandin synthesis, thereby exerting anti-inflammatory, analgesic, anti-exudative and antipyretic effect.

It can be accepted that the pharmacodynamic properties of meloxicam in the reference product have already been adequately characterised and that cross-reference to the dossier of the reference product would be appropriate.

Pharmacokinetics

In support of this application, the applicant conducted an in vivo bioavailability study in order to compare the plasma concentration profile of meloxicam between the candidate formulation Loxitab 2.5 mg tablets and the reference product Metacam 1.5 mg/ml oral suspension for dogs.

Bioequivalence studies

The applicant provided the results of an in vivo bioequivalence study conducted using the 2.5 mg tablet strength candidate and the 1.5 mg/ml oral suspension strength reference formulation. In order to bridge data from the reference product Metacam 1.5 mg/ml oral suspension for dogs to the strength of 1 mg, the applicant also performed a dissolution study (see part 2).

A single dose, two period, two sequence, crossover bioequivalence study of two meloxicam containing tablets after oral administration in beagle dogs:

This was a GLP compliant study using 16 beagle dogs. The study was designed as a cross-over study with two treatment periods (1 and 2) and a wash out period of 7 days between treatment periods. In treatment period 1, dogs in group 1 received the test product (Loxitab 2.5 mg tablets), whilst group 2 received the reference product (Metacam 1.5 mg tablets); in the second treatment period treatments swapped, i.e. dogs in group 1 received the reference product, whilst group 2 received the test product.

Animals were already acclimatised as they originate from the animals housed in test facility. Dogs were randomly assigned (8 animals in each group) based on gender and weight.

The test product was administered orally as "ready-to-use" tablet (1 tablet per animal) in the afternoon every period. The reference product was administered as "ready-to-use" suspension (1.67 ml per animal). After administration of the products, a small amount of water (approximately 5 ml) was given to ensure correct intake of the tablet/suspension.

Blood samples for plasma meloxicam determination were collected from the jugular vein on 18 occasions in each period of the study.

Samples were assayed for the determination of meloxicam content using a LC-MS/MS method validated in the concentration range 25 – 5000 ng/ml.

The plasma concentrations of meloxicam were used to calculate the pivotal pharmacokinetic parameters C_{max}, T_{max}, T_{last}, $AUC_{last,}$ $T_{1/2\ and}$ AUC_{∞}.

Determination of bioequivalence was based on the pivotal parameters C_{max} and AUC_{last}. Demonstration of bioequivalence was specified as having been achieved if the 90% confidence intervals for AUC_{last} are within the ratio of the test mean to control mean of 0.8 to 1.25 and if the 90% confidence intervals for C_{max} are within the ratio of 0.7 to 1.43. The wider acceptance limits of 70 – 143% for the confidence interval for C_{max} were chosen by the applicant based on the expected variability of C_{max}. This was accepted by CVMP.

The peak concentration, C_{max}, was reached at 2 to 14 hours after dosing of the reference product (758 ng/ml) and 1 to 10 hours after dosing of the test product (760 ng/ml). T_{last} ranged between 72 to 96 hours for the reference product and 72 to 96 hours for the test product. Terminal half-life was 21.7 hours after dosing of the reference product and 23.1 hours after dosing of the test product.

The results of the comparative bioavailability study indicate that the 90% confidence intervals for the estimate of the ratio of the means for AUC_{last} (95 – 103%) lie within the narrower limits of 80% to 125% and fell within the widened acceptance limits of 70 – 143% for C_{max} (95-109%).

Therefore, based on the results presented it can be concluded that the two articles are bioequivalent.

Target animal tolerance

In accordance with the legal basis of the application and because bioequivalence has been demonstrated between the test and reference products, the applicant is not required to provide any data on target animal safety.

Overall conclusion on efficacy

In accordance with the legal basis of the application, the applicant has not submitted any data on pharmacodynamics, target animal safety or clinical field trials. This is considered acceptable.

In support of the efficacy of the product, the applicant conducted an in vivo bioequivalence study to compare the pharmacokinetic profile of the test product with the reference product.

In the two-period, two-sequence, single dose, crossover bioequivalence study, the 90% confidence interval for the ratio of means (test/reference product) fell within the accepted confidence interval of 80 -125% for AUC_{last} and fell within the widened acceptance limits of 70 – 143% for C_{max}. The

widening of the acceptance limit for C_{max} is accepted on the expected variability of the active substance. The wider acceptance limits were pre-specified in the study plan.

Consequently, the characteristics of the product with reference to the efficacy and target animal tolerance are considered to be the same for the test and reference product.

The SPC includes the same information as that of the reference product Metacam 1.5 mg/ml oral suspension for dogs. As both oral forms differ in pharmaceutical form, the corresponding SPC sections were amended by the applicant.

Part 5 – Benefit-risk assessment

Introduction

Loxitab is a tablet containing meloxicam, an active substance which is well-known.

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class which acts by inhibition of prostaglandin synthesis, thereby exerting anti-inflammatory, analgesic, anti-exudative and antipyretic effects.

The product is intended for use in dogs for alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders.

The proposed posology of a single dose of 0.2 mg meloxicam/kg body weight on the first day followed by a maintenance dose of 0.1 mg/kg body weight once daily by oral administration (at 24-hour intervals) has been confirmed.

The application has been submitted in accordance with Article 19(1) of Regulation (EU) 2019/6 (hybrid application) as the quantitative composition of the active substance in Loxitab is different to that in the reference product (Metacam 1.5 mg/ml oral suspension for dogs).

Benefit assessment

Direct benefit

The active substance, meloxicam, is a well-known non-steroidal anti-inflammatory drug in veterinary medicine. It is beneficial in the alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders in dogs.

The evidence for the benefit is considered established on the basis of bioequivalence to the reference product when administered at the same dose, route of administration and dosing interval as recommended in the marketing authorisation for the reference product.

Additional benefits

None.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety

Risks for the target animal

Loxitab tablets is not expected to pose a risk for the target animal when used according to the SPC recommendations. The main reported adverse reactions stated in SPC include gastro-intestinal, renal and hepatic disorders. As with other NSAIDs, serious adverse effects can occur and, in very rare cases, may be fatal. The safety of the veterinary medicinal product has not been established during pregnancy and lactation.

Risk for the user

Loxitab 1 mg and 2.5 mg tablets for dogs are not expected to pose a risk for the user when used according to the SPC recommendations. The composition in excipients differs from that of the reference product, but this does not present a safety concern. The main reported adverse reactions stated in the SPC include hypersensitivity to NSAIDs and adverse effects after accidental ingestion of the product. The most severe risk is accidental ingestion by a child. An appropriate warning is included in the SPC.

Risk for the environment

Loxitab 1 mg and 2.5 mg tablets for dogs is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user, environment and to provide advice on how to prevent or reduce these risks.

User safety

User safety risks have been identified, mainly the risks associated with exposure in children. These risks are mitigated by including the warning to keep the product away from children. Appropriate measures are included in section 3.5 of the SPC.

Conditions or restrictions as regards the supply or safe and effective use of the VMP concerned, including the classification (prescription status)

The veterinary medicinal product is subject to a veterinary prescription.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication: Alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders in dogs.

The product has been shown to be efficacious for these indications, and the CVMP accepted the indications as proposed by the applicant.

Based on the data presented to date, the overall benefit-risk balance is considered positive.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

It is well tolerated by the target animals and presents an acceptable risk for users and the environment, when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

The product information has been reviewed and is considered to be satisfactory and in line with the assessment.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Loxitab is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 2019/6).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.