6 October 2022
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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for an extension to the marketing authorisation for Meloxoral (EMEA/V/C/000151/X/0015)

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 Dechra Regulatory B.V submitted on 3 September 2021 an application for an extension to the marketing authorisation for Meloxoral to the European Medicines Agency (The Agency) in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I thereof.

Meloxoral is a generic veterinary medicinal product for which the reference product is Metacam.

Meloxoral is currently authorised as an oral suspension in two strengths - 0.5 mg/ml for use in cats and 1.5 mg/ml for use in dogs. It contains meloxicam, a non-steroidal anti-inflammatory drug (NSAID) and was authorised for use in the Union on 19 November 2010.

This extension application is a new pharmaceutical form, chewable tablets, in three new strengths, 1.0 mg, 2.5 mg and 4.0 mg, for use in dogs.

The applicant applied for the following indication:

Alleviation of inflammation and pain in both acute and chronic musculoskeletal disorders.

Meloxoral chewable tablets contain 1.0 mg, 2.5 mg and 4.0 mg meloxicam and are presented in packs containing 30, 50 and 100 tablets.

The rapporteur appointed is Andrea Christina Golombiewski and the co-rapporteur is Leona Nepejchalová.

The dossier has been submitted in line with the requirements for submissions in accordance with Article 19 of Commission Regulation (EC) 1234/2008 and Annex I thereof (extensions).

On 6 October 2022, the CVMP adopted an opinion and CVMP assessment report.

On 30 November 2022, the European Commission adopted a Commission Decision approving the extension to the marketing authorisation for Meloxoral.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

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Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (dated 01 February 2019) which fulfils the requirements of Directive 2001/82/EC. 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

Batch release takes place within the EEA at Lelypharma B.V., Netherlands. The site has a manufacturing authorisation (MIA-No.: 2004-FGL) issued on April 16th 2019 by the competent authority of the Netherlands. GMP certification is provided and confirms the date of the last inspection (17th June 2020) which shows that the site is authorised for batch release of such veterinary dosage forms. Manufacture, control testing and packaging takes place within the EEA and appropriate certification is provided.

A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU manufacturing and batch release site. The declaration was based on an on-site audit on 11th to 13th November 2019. The date of the on-site audit does not exceed 3 years.

The GMP certificate for meloxicam was issued by the competent authority of Italy following inspection of the manufacturer. The GMP Certificate of (manufacturer of the active substance, testing, release and packaging) which is included in the concerned dossier, has an inspection date of 22nd February 2018.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

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

Part 2 - Quality

Composition

Meloxoral chewable tablets are hybrid medicinal products of the reference medicinal product Metacam 1.5 mg/ml oral suspension for dogs - MAH Boehringer Ingelheim Vetmedica GmbH as authorised by the Community.

The product is presented as light brown, slightly dotted, circular, biconvex chewable tablet containing the active substance meloxicam in three strengths: 1 mg/tablet, 2.5 mg/tablet and 4 mg/tablet of the active substance respectively. The other ingredients are microcrystalline cellulose, crospovidone (type A), lactose monohydrate, magnesium stearate, colloidal hydrated silica, sodium citrate and the flavouring agents chicken flavour and yeast extract (dried).

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Containers

The tablets are packaged in an aluminium / aluminium blister within an outer carton. The packaging material complies with the relevant EU requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The bulk container used for storage of the tablet cores is a double medium-density polyethylene (MPDE) bag, with a desiccant sachet placed between both bags.

Development pharmaceutics

The tablets used for the stability studies and for product registration were manufactured according to the same manufacturing process (blending and direct compression) used in the manufacture of the clinical trial formulation. However, there is a difference in the formulation between the clinical batches and the final formulation. The active substance meloxicam used in the proposed formulation is manufactured at the proposed active substance manufacturing site, whereas the meloxicam used in the clinical trial batches was manufactured at a different active substance manufacturing site. The comparative data on the particle size distribution and on the polymorphic form as well as comparative dissolution profiles between the finished product manufactured with the active substance from both suppliers fully demonstrate that both manufacturers produce a comparable quality of the active substance.

Direct compression technology was selected for the formulation. Derivation of the formulation is logical and described in the dossier and the formulation components are commonly used in this dosage form. The function of the excipients in the formulation is discussed. Although not all excipients are of pharmacopoeial grade, all can be considered 'standard' excipients that are commonly used in veterinary medicinal products and their use can be accepted. The suitability of the manufacturing method was supported by a validation study conducted on two production-scale batches. The results of the validation study are discussed in Part 2.B. The generation of degradation products was discussed in detail in the development part.

Investigation of the dissolution test is described. Bioequivalence of the 2.5 mg tablet with the reference product is demonstrated by an *in vivo* bioequivalence study (see Part IV). The applicant has performed comparative dissolution testing of the 2.5 mg strength against the 1.0 mg and the 4.0 mg strength at pH 1.2, 4.5 and 7.5. The similarity factor f2, as per the 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' EMA/CVMP/016/2000-Rev.3, was also calculated for each of the profiles, results were within 50 – 100, suggesting that the dissolution profiles are similar.

Each tablet has a cross-shaped break mark. Compliance of two production scale batches of each strength of product with the Ph. Eur. requirements for subdivision of tablets has been shown (halves and quarters of tablets).

Method of manufacture

The tablets are manufactured using direct compression. All tablet strengths are produced from a common blend. The manufacturing process is well described. Details on bulk holding times, the used equipment and the container for the bulk product were provided. In-process controls are adequate for this type of manufacturing process and the pharmaceutical form. The manufacturing process is regarded as a non-standard process because of the low content of active substance in the formulation (≤ 2%). Comprehensive validation of the manufacturing process for each tablet

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strength has been conducted on two production scale batches and the data provided demonstrates that all critical parameters are within acceptable limits, and that a quality product is consistently produced. The batch size range is larger than the production scale batches but was accepted even though the tablets contain the active substance in low content as the tablets are manufactured using a conventional process including well-established technologies, all batch sizes are manufactured using similar production equipment and the finished product manufacturer already produces tablets containing the active substance in low content under GMP compliance for a prolonged period of time. The applicant confirms that process validation studies will be performed when the batch size deviates above the production batch size. These validation(s) will be done according to the process validation scheme as presented in the dossier and data will be provided immediately to the competent authorities if outside specifications (with proposed action). A validation scheme for the third planned production batch has been provided.

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Control of starting materials

Active substance

The active substance meloxicam is monographed in the Ph. Eur. and data on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

The active substance specification of the finished product manufacturer includes tests for appearance, solubility, identity (IR), polymorphic form, assay (potentiometric titration), impurities (HPLC), residual solvents (GC), loss on drying, sulphated ash and particle size (laser light diffraction).
Batch analysis data on the active substance have been provided, showing compliance with the active substance specification. A re-test period of 5 years for meloxicam is accepted.

The submitted Applicant's Part and Restricted Part versions for meloxicam were accepted in a concurrent procedure for the oral solution which concluded in December 2021. The consolidated version of the ASMF including all changes made during the concurrent procedure, dated November 2021, was submitted by the ASMF holder.

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 EMEA/CVMP/004/98-final 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. Suitable limits for functionality related characteristics are included in the specifications of the excipients. The list of excipients is included in section 6.1 of the SPC.

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

Declarations regarding TSE are provided in Part I and Part IIC. An annex III declaration for the product is provided in Part I. A declaration is provided by the active substance supplier that meloxicam does not contain, or use during manufacture, any materials of bovine, ovine or caprine origin. Furthermore, appropriate declarations are provided for the excipients.

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Control tests during production

Not applicable.

Control tests on the finished product

The finished product release specification controls relevant parameters for the dosage form. Parameters on the specification are appearance, dissolution, tablet mass, resistance to crushing, uniformity of dosage units, identification of the active substance, assay, friability, related substances and microbiological testing. Suitable method descriptions have been provided. The validations of the analytical methods for determination of assay of meloxicam and related substances as well as for dissolution testing are in accordance with the VICH guideline GL2 'Validation of analytical procedures: Methodology'.

Suitability of the method for microbiological quality has been proven. A full risk assessment on elemental impurities was provided.

Batch analysis data is provided for the two process validation batches covering each tablet strength. The data are comparable between batches, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.
A certificate of the primary reference standard for meloxicam used for testing of the finished product was provided.

Stability

The proposed specification for shelf life is the same as that for release except for widened limits for resistance to crushing of the tablets and for total impurities.

Stability data of the two validation batches of finished product stored under long term conditions for 36 months at 25 ºC/60% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH guideline GL3 were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. As the tablets are compressed from a common blend, a bracketing approach in accordance with VICH GL45 was used testing only the extreme strengths.

Samples were tested for appearance, content of active substance, related substances, microbiological quality, resistance to crushing and dissolution. The analytical procedures used are stability indicating. All results are in compliance with the currently proposed specification. Although there have been noted some slight trends in assay and related substances no significant changes are observed. The physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SPC. The applicant confirmed that they will perform VICH stability studies on one further production batch in part II.F. of the dossier.

In-use testing of the tablets was performed and an in-use stability of 3 days is acceptable. No photostability studies were performed as the packaging material is protective against light and the in-use study for quarter tablets was performed unprotected from daylight. No significant changes in product quality were observed during in-use stability testing.

Based on the available stability data, the proposed shelf-life of 3 years and an in-use shelf-life of the divided tablets of 3 days without a storage condition as stated in the SPC are acceptable.

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Overall conclusions on quality

The information in Part II of the dossier corresponds to current rules and guidelines.

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. The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way. Justification regarding formulation of the product supported by suitable data has been provided. Comparison of the quality of the active substance, used for the clinical trial batches, and the active substance, used for the proposed formulation, in order to demonstrate their comparability was performed.

The manufacturing process is classified as a non-standard process as the product contains the active substance meloxicam in a low content (≤ 2% of composition) even though direct compression is a simple process. A detailed description of the manufacturing process has been provided along with relevant in-process controls. Process validation data has been provided for two full scale finished product batches and the data provided demonstrates that all critical parameters are within acceptable limits, and that a quality product is consistently produced. The proposed batch size range is accepted even though the active substance meloxicam is contained in a low content (≤ 2% of composition) as the tablets are manufactured using a conventional process including well-established technologies, all batch sizes are manufactured using similar production equipment and the finished product manufacturer already produces tablets containing the active substance in low content under GMP compliance for a prolonged period of time. Process validation studies will be performed when the batch size deviates from the production batch size. A validation scheme for the third planned validation batch size has been provided.

The active substance meloxicam is monographed in the Ph. Eur. and data on the active substance is provided in the form of an Active Substance Master File. Stability data has been provided for the active substance. The specification controls relevant parameters of the active substance. Batch analysis data has been provided. Information on the active substance is detailed in separate reports for the Applicant's Part and the Restricted Part (AP/RP - November 2021, version 2) that have been assessed and accepted in a concurrent procedure. Suitable specifications were established for the excipients. Acceptable information has been provided for the container-closure systems. Data has been presented to give reassurance on TSE safety.

The finished product release specification controls relevant parameters for the dosage form. The analytical validations of the control methods are acceptable.

Stability data has been provided for the finished product. A shelf-life of 3 years and an in-use shelf-life of divided tablets of 3 days without a storage condition are considered acceptable. The information in Part II of the dossier corresponds to current rules and guidelines. Information on the development, manufacture, control of the active substance, control of the finished product and stability has been presented in a satisfactory manner.

Based on the review of the data on quality, the manufacture and control of Meloxoral chewable tablets are considered acceptable.

The applicant has confirmed that they will perform process validation studies on one further commercial batch and when the batch size deviates above this batch size. Furthermore, the applicant has confirmed that they will place one additional production batch, to a total of at least three batches, on long-term stability studies through the proposed shelf life and on accelerated

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studies for 6 months.

Part 3 – Safety

Safety documentation

Meloxoral 1.0 mg, 2.5 mg, and 4.0 mg chewable tablets contain meloxicam as active substance and are indicated for the alleviation of inflammation and pain in both acute and chronic musculoskeletal disorders in dogs.

This application has been submitted in accordance with Article 13(3) of Directive 2001/82/EC, as amended. Metacam 1.5 mg/ml oral suspension for dogs, first authorised by the European Commission in 1998, has been chosen as reference product.

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. Regarding the excipients, the differences noted between the formulations do not represent a safety concern. A user risk assessment (URA) has 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).

User safety

The applicant provided a user risk assessment (URA), which is in line with relevant EMA guidance (EMA/CVMP/543/03-Rev.1). The URA includes hazard identification and characterisation, exposure assessment, and a qualitative and quantitative risk characterisation as well as suggestions for risk mitigating measures for the according sections of the product literature. No new toxicological data or information on the active ingredient or excipients of the candidate product are presented. To substantiate the URA, the applicant relies on toxicity data from the CVMP summary report of meloxicam (EMEA/MRL/571/99-FINAL). The SPC of Melcam 7.5 mg tablets, a human medicinal product containing the same active substance, is provided as supportive information.

The main potential routes of accidental contact with the product were assessed and it was concluded that direct dermal exposure and indirect oral exposure through hand-to-mouth contact (non-professional adult user) and accidental ingestion (child) are most likely.

It is considered likely that adverse events will not occur as a result of the total exposure of the non-professional adult user, as the toxicological ADI for meloxicam (i.e. 1.25 µg/kg bw) is not exceeded. However, due to the expected daily exposure of the user and potential hypersensitivity reactions, appropriate warnings are included in the product information.

With regard to accidental oral ingestion by a child, the applicant has considered the ingestion of half a 4.0 mg tablet by a child of 12.5 kg as a worst-case scenario. Comparing this value with the lowest oral NOEL of 0.2 mg/kg bw, based on a 52-week feeding study in rats (EMEA/MRL/571/99-FINAL), the margin of exposure is below the trigger value of 100. Even if this NOEL is based on a chronic dose toxicity study and the accidental exposure is considered as a single exposure, this is considered a not acceptable risk. Therefore, the applicant proposed additional user warnings in the product literature in order to mitigate the risk for the child.

In addition, the applicant proposed to amend the initial user warnings of the reference product both

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according to the ABCD format and to address potential hypersensitivity reactions caused by the excipients.

As a result of the user safety assessment the following warnings for the user are considered appropriate:

- This veterinary medicinal product may cause hypersensitivity reactions. People with known hypersensitivity to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or to any of the excipients should avoid contact with the veterinary medicinal product.
- Accidental ingestion, especially by children, may cause adverse reactions. Unused tablet parts should be placed back into the blister and carton and carefully kept away from children. In case of accidental ingestion by a child seek medical advice immediately and show the package leaflet or the label to the physician.
- Wash hands after use.

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.

Environmental risk assessment

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

The ERA can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food animals. The product, Meloxoral 1.0 mg, 2.5 mg, and 4.0 mg chewable tablets for dogs, is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

The application for Meloxoral 1.0 mg, 2.5 mg, and 4.0 mg chewable tablets has been submitted in accordance with Article 13(3) of Directive 2001/82/EC, as amended. 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.

An URA in line with the relevant guidance document has been presented. The worst-case scenario for user safety is ingestion of half a 4.0 mg tablet by a child, with an estimated margin of exposure of 1.25. Appropriate safety warning statements are included in the SPC to mitigate the risks.

An ERA conducted in accordance with the relevant VICH and EMA guidelines has been provided. As Meloxoral is intended for single use in dogs, a non-food-producing animal, the ERA can stop at Phase I and a Phase II assessment is not required.

The CVMP concluded that Meloxoral 1.0 mg, 2.5 mg, and 4.0 mg chewable tablets are not expected to pose a risk to the user and to the environment when used in accordance with the SPC.

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Part 4 – Efficacy

Pharmacodynamics

The application is made in accordance with Article 13(3) of Council Directive 2001/82/EC (as amended), for a hybrid product, and as bioequivalence has been demonstrated, data on pharmacodynamics are not required. The SPC section on pharmacodynamics is still valid and correct and has not been updated.

Pharmacokinetics

The applicant has provided two bioequivalence studies (a pilot non-GLP study and a pivotal GLP study) in support of this extension to the Community marketing authorisation via the centralised procedure.

Bioequivalence studies

The applicant has performed one pilot and one pivotal bioequivalence study.

In order to investigate the bioavailability and to be able to select a reference product, in the three-armed non-GLP pilot study, the test item Meloxoral 2.5 mg chewable tablets for dogs was compared to Metacam 1.5 mg/ml oral suspension for dogs (reference item 1) and Metacam 2.5 mg chewable tablets for dogs (reference item 2). The 90% confidence intervals for the test/reference ratios of the geometric least squares means calculated for C_{max} (93% - 117%) and AUC_{0-t} (86%- 114%) were within the bioequivalence acceptance criteria of 80% – 125% for reference item 1 (suspension) and AUC_{0-t} (92% - 122%) of reference item 2, but not for C_{max} (103% - 129%) of reference item 2 (tablets).

Based on these results, it was decided to conduct the pivotal bioequivalence study with Metacam 1.5 mg/ml oral suspension, which is considered acceptable.

Bioequivalence of Meloxoral 2.5 mg chewable tablets for dogs and Metacam 1.5 mg/ml oral suspension for dogs (Boehringer Ingelheim Vetmedica GmbH, Germany) was successfully demonstrated in an appropriately designed and performed randomised, two-period, two-sequence single dose crossover GLP-study including a total of 16 beagle dogs (1-6 years old, 10.8-13.8 kg): the sampling time points were adequately chosen and allowed reliable estimates for C_{max} and AUC; also the washout period was sufficiently long. There were no significant period or sequence effects. The confidence intervals for the C_{max} and AUC ratios (90% - 108% and 89% - 105%, respectively) were well within the pre-defined acceptance regions. In conclusion, bioequivalence of the test product Meloxicam 2.5 mg chewable tablets for dogs and the reference item (Metacam 1.5 mg/ml oral suspension) was demonstrated.

Target animal tolerance

The application is made in accordance with Article 13(3) of Council Directive 2001/82/EC (as amended), for a hybrid product; as bioequivalence has been demonstrated, toxicological data are not required. The applicant has included the same warnings in the SPC and product literature, as that of the reference product, Metacam 0.5 mg/ml oral suspension. No adverse reactions with the candidate product were observed in the bioequivalence studies.

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Overall conclusion on efficacy

Pharmacodynamics, Pharmacokinetics, Tolerance, Efficacy:

This is an application according to Article 13(3) of Directive 2001/82/EC as amended. Bioequivalence between the candidate product Meloxoral 2.5 mg chewable tablets for dogs and the reference product Metacam 1.5 mg/ml oral suspension for dogs (Boehringer Ingelheim Vetmedica GmbH, Germany) after oral administration in dogs can be considered to have been established according to the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.3-corr.).

For the additional strengths (1 mg, 4 mg), in vitro equivalence to the 2.5 mg strength could be demonstrated with in vitro dissolution data. Based on the type of application, pharmacodynamic, pharmacokinetic, tolerance and efficacy studies are not required. The dosage, route of administration, target animal species and indication of this product is identical to the reference product.

Part 5 – Benefit-risk assessment

Introduction

The product Meloxoral chewable tablets for dogs contains meloxicam as the active substance. This procedure is an extension of the approved Meloxoral oral suspension for dogs to introduce a new dosage form (1 mg, 2.5 mg and 4 mg chewable tablets).

Benefit assessment

Direct therapeutic benefit

The product is indicated in dogs for alleviation of inflammation and pain in both acute and chronic musculoskeletal disorders. Efficacy has been demonstrated by means of bioequivalence to the reference product Metacam 1.5 mg/ml oral suspension for dogs (Boehringer Ingelheim Vetmedica GmbH, Germany).

Additional benefits

Meloxoral chewable tablets for dogs are easy to administer by the owner.

Risk assessment

The safety to users of the product and to the target species can be assumed from the reference product. None of the excipients would indicate an increased safety risk. It is concluded that the candidate product does not pose an unacceptable risk to the user when used in accordance with the SPC. The use of the product is not expected to pose a risk for the environment.

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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, the environment and to provide advice on how to prevent or reduce these risks.

User safety risks have been identified, mainly the risks associated with exposure via direct dermal exposure and indirect oral exposure through hand-to-mouth contact (non-professional adult user) and accidental ingestion (child). These risks are mitigated by user safety warning sentences in SPC.

Evaluation of the benefit-risk balance

Since bioequivalence of the candidate and reference product can be accepted, the benefit-risk balance of the candidate product is considered favourable when used according to the labelling. Information included in the SPC and other product information is consistent with the reference product and appropriately informs on the potential risks of this product relevant to the target animal, user and environment and to provide advice on how to prevent or reduce these risks.

Conclusion

Based on the demonstration of bioequivalence to the reference product, it is considered that the application for the product is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

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.

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