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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a grouped variation requiring assessment for Daxocox (EMEA/V/C/005354/VRA/0003/G)

INN: Enflicoxib

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

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Introduction

Submission of the variation application

In accordance with Article 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Ecuphar NV (the applicant), submitted to the European Medicines Agency (the Agency) on 2 April 2024 an application for a group of variations requiring assessment for Daxocox.

Scope of the variation

Daxocox is already authorised for use in dogs for the treatment of pain and inflammation associated with osteoarthritis (or degenerative joint disease). Daxocox tablets contain 15, 30, 45, 70 or 100 mg of enflicoxib and are presented in packs containing 4, 10, 12, 20, 24, 50 or 100 tablets.

Variations requested	
I.II.1.c	Changes to strength, pharmaceutical form and route of administration - Change or addition of a new strength/potency
G.I.4	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.

This grouped variation is to add two new tablet strengths (140 and 200 mg) and to amend the dosing table for the currently approved tablet strengths (15, 30, 45, 70 and 100 mg).

Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 2, Part 3, Part 4.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided an updated 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) with reference number PSMF-22-ANIMALCAREGROUP, 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

Manufacture of the active substance enflicoxib takes place outside the EEA. A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site manufacturer of dosage form. The declaration was based on an onsite audit by a third party.

GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the activities indicated above, has been provided.

Finished product

Batch release of the finished product takes place at Lelypharma B.V., the Netherlands. The site has a manufacturing authorisation issued on 7th November, 2023 by the competent authority of the Netherlands. GMP certification, which confirms the date of the last inspection and shows that the site is authorised activities indicated above, has been provided.

Overall conclusions on administrative particulars

The summary of 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 finished product is presented as brown, round and convex or capsule shaped tablets containing the active substance enflicoxib in 7 tablet strengths: 15 mg, 30 mg, 45 mg, 70 mg, 100 mg, 140 mg (added with this variation application) and 200 mg (added with this variation application). The other ingredients are silicified microcrystalline cellulose, mannitol, sodium laurilsulfate, crospovidone, dried flavour, pigment blend, copovidone, sodium stearyl fumarate and talc.

Containers and closure system

Cross-reference is made to data already submitted and assessed for this marketing authorisation, for the original 15 mg, 30 mg, 45 mg, 70 mg and 100 mg tablet strengths by the CVMP previously, and no new data on quality were submitted for the container-closure system. This is considered acceptable.

Product development

The tablets used in the clinical trials consisted of a range of 3 divisible tablets, whereas the final formulations consist of 7 non-divisible tablets. 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 trials formulation. However, there is a minor difference in the formulation between the clinical batches and the final formulation in that the flavouring agent was changed from 'beef liver roasted flavour' to 'dried flavour' due to the discontinuation of the beef liver roasted flavour. The two flavours have similar characteristics, and are present at the same concentration in the two formulations. In addition, active substance used in the proposed formulation is manufactured at the proposed active substance manufacturing site with an optimised route of synthesis, whereas that used in the clinical trial batches was manufactured at a different active substance manufacturing site by a previous route of synthesis. Comparative batch analytical data has been provided for the batch of the active substance used in the clinical trial batches and three batches of the active with the optimized process used for the proposed formulation and the results comply with the updated active substance specification, and are

comparable between batches and between sites. Comparative pXRD data is provided on the same four batches, demonstrating that all have the same polymorphic form. Comparative specific optical rotation data has been provided for the same four batches indicating that both routes of synthesis produce the same racemic mixture. In addition, justification of the choice of a racemate instead of a single enantiomer has been provided. Comparative particle size data has been provided for the batch of the active substance produced used in the clinical trial batches and three batches of the active with the optimized process used for the proposed formulation and the results are comparable between batches and between sites. In addition, confirmation has been provided that the particle size of the batches of mannitol used in the clinical trial batches also complied with the proposed particle size limits for this excipient.

Direct compression technology was selected for the formulation due to its simplicity. Derivation of the formulation is logical and well described in the dossier and the formulation components are commonly used in this dosage form. The function of each excipient is clearly detailed and their selection was based on screening studies based on the rheological characteristics and ability to enhance the solubility of the active substance.

Investigation of the dissolution test is described. Comparative dissolution testing was performed for the 120 mg tablets used in the clinical trials versus batches of the 15 mg, 30 mg, 45 mg, 70 mg, 100 mg, 140 mg and 200 mg product strengths 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, was also calculated for each of the profiles, and were within 50 – 100, suggesting that the dissolution profiles are similar. It was confirmed that the conditions followed for the evaluation of the similarity factor are in line with the requirements of the 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' EMA/CVMP/016/2000. Information has been provided on the discriminatory nature of the dissolution method, including detail on the manufacture of a 'bad batch' in which changes were made to the proportion of excipients and its resultant dissolution profile. The proposed limit for the finished product dissolution test is in line with the recommendations of the 'Reflection paper on the dissolution specification for generic oral immediate release products with systemic action' EMA/CHMP/CVMP/QWP/226031/2017, enhancing the discriminatory nature of the dissolution method.

Description of the manufacturing method

The manufacturing process is a standard direct compression process. A premix is mixed, sieved and mixed again. The remaining sieved ingredients are then added to the premix blend and mixed. The final bulk blend is then sieved and compressed into tablets. The tablets are packed into blisters, packed into cartons, and a final inspection is carried out. In-process controls are adequate for this type of manufacturing process and pharmaceutical form. Process validation data has been provided for three full scale finished product batches of the 15 mg, 30 mg, 45 mg, 70 mg and 100 mg tablet strengths, and two full scale finished product batches of the 140 mg and 200 mg tablet strengths. The data provided demonstrates that all critical parameters are within acceptable limits, and that a quality product is consistently produced, and acceptable validation data has also been provided to support the 4-month bulk hold time for the tablets.

Control of starting materials

Cross-reference is made to data already submitted and assessed for this marketing authorisation, for the original 15 mg, 30 mg, 45 mg, 70 mg and 100 mg tablet strengths by the CVMP previously, and no new data on quality were submitted for the control of starting materials. This is considered acceptable.

Control tests on the finished product

The finished product release specification controls relevant parameters for the dosage form. Parameters on the specification are: appearance, uniformity of dosage units, identification of the active substance and of the pigment, assay, related substances, dissolution, average tablet weight and microbiological testing. The validation of the analytical methods is in accordance with the VICH guideline GL2 'Validation of analytical procedures: Methodology'. Batch analysis data is provided for three full scale process validation batches of the 15 mg, 30 mg, 45 mg, 70 mg and 100 mg tablet strengths, and two full scale finished product batches of the 140 mg and 200 mg tablet strengths. The data demonstrates compliance with the proposed specifications and are comparable between batches. Information is provided on the reference standards used in the testing of the finished products.

Stability

The proposed specification for shelf life is the same as that for release with the following exception: uniformity of dosage units.

A stability study was conducted with three full scale process validation batches each of the lowest (15 mg) and median (45 mg and 100 mg) strengths of tablets, and two batches each of the highest (200 mg) strength of tablets. As the tablets are compressed from a common blend, a partial bracketing approach in accordance with VICH GL45 was used. The batches were packaged in Alu/Alu blisters, however the lidding foil used in the stability studies for the 15 mg, 45 mg and 100 mg strengths did not include the paper and polyethylene layers that are present in the proposed packaging, and so the blister used in the stability studies is considered worst-case in comparison to the proposed commercial packaging, which is acceptable. The 200 mg strength tablets are packaged in child-resistant aluminium-sealed aluminium blister strips.

Samples of the 15 mg, 45 mg and 100 mg strengths were stored at 25ºC/60% RH, 30ºC/65% RH and 40ºC/75% RH according to VICH GL3 and stability data is available to 48 months. Samples of the 200 mg strength were stored at 30ºC/65% RH and 40ºC/75% RH according to VICH GL3 and stability data is available to 6 months. The studies are scheduled to continue up to 60 months. All results are in compliance with the currently proposed specification. Although there have been some trends noted in assay and dissolution, there is only minor trending apparent. The provided stability data supports the shelf-life of 4 years with no special temperature storage conditions. No photostability studies have been provided, which is accepted as the blister packaging will provide adequate protection from light, and so, the storage condition of "Store in the original package in order to protect from light" is included in the relevant sections of the SPC and product literature.

Overall conclusions on quality

Information on the development, manufacture and control of the active substance and the finished product is satisfactory.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics.

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. Information relating to the discriminatory nature of the dissolution test has been provided, along with amended limits for dissolution to ensure batches continue to display dissolution properties similar to that of clinical trial batches.

The manufacturing process is a standard one. A detailed description of the manufacturing process has been provided along with relevant in-process controls. Process validation data has been provided for 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.

Cross-reference is made to data already submitted and assessed for this marketing authorisation, for the original 15 mg, 30 mg, 45 mg, 70 mg and 100 mg tablet strengths by the CVMP previously, and no new data on quality were submitted for the control of starting materials.

The finished product release specification controls relevant parameters for the dosage form.

Stability data has been provided for the active substance and finished product. The provided stability data supports the proposed shelf-life of 4 years with no special temperature storage conditions, but including a labelling requirement for photo-sensitivity.

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. Based on the review of the data on quality, the manufacture and control of the product are considered to be acceptable.

Part 3 – Safety

Daxocox (containing 15, 30, 45, 70 or 100 mg of the active substance enflicoxib) is authorised for use in dogs for the treatment of pain and inflammation associated with osteoarthritis (or degenerative joint disease).

This grouped variation is to add two new tablet strengths (140 and 200 mg) to the existing range for the purpose of facilitating treatment of larger dogs, and to amend the dosing table for the currently approved tablet strengths (15, 30, 45, 70 and 100 mg).

Cross-reference is made to data already submitted and assessed for this marketing authorisation by the CVMP previously, and no new data on safety were submitted, except for a user risk assessment update. Only new data have been assessed in the sections below.

Noting that the proposed new tablet strengths will be used in the target species dogs at the same posology and dosing interval as those strengths already authorised, it is accepted that the new tablet strengths will present no greater risk to the target animal, or to the environment, than the authorised strengths.

User safety

The applicant has provided an update to the user risk assessment that was presented and assessed by the CVMP in the context of the original MAA for Daxocox (in procedure number EMEA/V/C/005354). The update presented by the applicant takes into account the risk posed to a user by the proposed new tablet strengths that are the subject of this variation procedure (140 mg and 200 mg) and also, the conclusions reached by the CVMP upon assessment of the original URA (specifically in respect of selection of a suitable TRV for the calculation of margins of exposure).

With regard to hazard identification and characterisation, the applicant makes reference to the toxicological data already presented and assessed by the CVMP. In doing so, the applicant concludes that the hazard identification and characterisation for the active substance (enflicoxib) and excipients contained in the new proposed tablet strengths does not differ from that for the authorised tablet strengths. As the proposed

tablet strengths will be manufactured from the same common blend tablet mix and by the same manufacturing process that is used to produce the authorised 15, 30, 45, 70 and 100 mg tablet strengths, this conclusion is supported. It is also noted that the final formulation is accepted as being non-irritant to skin and eyes and is not a skin sensitiser.

Concerning risk, the applicant contends that, as the proposed new tablet strengths are non-divisible and are to be used at the same posology and dose interval (i.e. weekly) as the authorised tablet strengths, the same tasks and situations will lead to exposure, noting that no part tablets will require storage between administrations.

The same users (that is, both professionals and non-professional animal owners and children) are identified by the applicant, and the risk to professional users is not considered to be significant. Accidental ingestion of a tablet of the highest strength (200 mg) is identified as the worst-case scenario, and other accidental oral exposure (e.g. by hand to mouth contact) is considered less likely, and to present a negligible risk.

The applicant has calculated margins of exposure (MOEs) using a previously accepted TRV for both a child (10 kg) and an adult (60 kg) accidentally consuming a 200 mg tablet and compared them to the MOEs for consumption of a 100 mg tablet in the same scenario. As was the case for accidental consumption of a 100 mg tablet, accidental consumption of a 200 mg tablet also poses a risk (based on a MOE < 100) to both a child, and an adult (MOEs of 0.08 and 0.5 respectively). Noting that the risk mitigation measures and user safety warnings that are currently in place for the authorised VMP were approved based on essentially the same risk, the applicant proposes that these should be sufficient to mitigate against risk posed by the new tablet strengths.

In particular, the following points are noted:

- The tablets are non-divisible (and no tablet parts will be stored between administrations).
- The tablets are presented in child-proof packaging (compliant with ISO [EN] 14375).
- The instruction to store the VMP out of the sight and reach of children will be printed on the outer packaging.

Relevant user safety warnings are included in the authorised SPC and are suitably presented in the recommended [ABCD] format. It is observed by the applicant that since marketing the VMP, no reports of accidental ingestion have been received via the appropriate pharmacovigilance channels.

The update to the risk assessment is in accordance with the relevant guideline (EMA/CVMP/543/03-Rev.1). The proposed, new tablet strengths contain more enflicoxib per tablet than those currently authorised, and therefore there exists the possibility that a child could accidentally consume 200 mg (as compared to 100 mg enflicoxib). However, it is acknowledged that the original assessment of user risk was also based on this scenario (i.e. accidental consumption of a tablet by a child) posing a risk. The risk mitigation measures as highlighted by the applicant (including non-divisible tablets, child-proof packaging and suitable warnings on the outer package) and the already authorised user safety warnings are considered suitable therefore for the proposed new tablet strengths, and the CVMP concludes that no further risk mitigation measures or user safety warnings are required to ensure user safety when using the 140 mg and 200 mg tablets.

It is noted that the approved safety warnings contain information concerning use of the VMP by pregnant people. As is the case with accidental ingestion by a child, the risk posed to this specific sub-group by the proposed new tablet strengths is considered to have been suitably mitigated against by the existing, approved user safety warnings.

Overall, it is concluded that, when the VMP is used in accordance with the SPC, the risk to the user is acceptable.

Overall conclusions on the safety documentation: safety tests

With regard to demonstrating safety of the proposed new tablet strengths (140 mg and 200 mg), the applicant has referred to the safety data already submitted and assessed by the CVMP in the context of the original MAA for Daxocox and has not presented further safety data with the exception of an update to the user risk assessment.

Noting that the proposed new tablet strengths will be made from the same tableting blend in the same manufacturing process as the already authorised tablet strengths, and as such, will contain the active substance (enflicoxib) and excipients in the same proportions, it is accepted that the same hazard profile exists for the proposed tablet strengths as for the authorised strengths.

Noting also that the new tablet strengths are intended for use at the same posology and dosing interval as those strengths already authorised, it is accepted that the same tasks and situations will result in exposure of the same users (i.e. both professional and non-professional users) to the proposed tablet strengths. The worst-case exposure scenario identified is accidental ingestion of the highest strength tablet by a 10 kg child and based on a margin of exposure calculation using a previously accepted TRV, a risk to a child in this scenario is identified (MOE < 100).

During the initial authorisation of Daxocox, a risk to a child was also identified following ingestion of a 100 mg tablet, and based on this conclusion, the following risk mitigation measures were considered acceptable:

- The tablets are non-divisible (and no tablet parts will be stored between administrations).
- The tablets are presented in child-proof packaging (compliant with ISO [EN] 14375).
- The instruction to store the VMP out of the sight and reach of children will be printed on the outer packaging.

Suitable user safety warnings are also included in the approved SPC in the recommended [ABCD] format.

The existing risk mitigation measures and approved user safety warnings are considered suitable to mitigate against the risk such a scenario would pose, and no further updates are considered necessary to ensure user safety. Overall, it is concluded that, when the VMP is used in accordance with the SPC, the risk to the user is acceptable.

Noting that the proposed new tablet strengths will be used in the target species dogs at the same posology and dosing interval as those strengths already authorised, it is accepted that the new tablet strengths will present no greater risk to the target animal, or the environment than the authorised strengths. Although there exists potential for exposure of a user to a greater amount of enflicoxib when using the higher tablet strengths (as compared to the authorised strengths), the potential risk to a user has been suitably mitigated against.

Overall, the approach of the applicant in respect of the data presented in support of safety of the proposed tablet strengths (140 and 200 mg) is considered acceptable.

Part 4 – Efficacy

This grouped variation is to add two new tablet strengths (140 and 200 mg) to the existing range for the purpose of facilitating treatment of larger dogs, and to amend the dosing table for the currently approved tablet strengths (15, 30, 45, 70 and 100 mg).

With regard to the addition of the two new strengths (140 and 200 mg), cross-reference is made to data already submitted and assessed for the marketing authorisation application by the CVMP previously, and no new data on efficacy were submitted.

Comparative dissolution testing was performed by the applicant. Based on these data, the dissolution profiles of the proposed tablet strengths (140 and 200 mg) are accepted as being similar to those of the 120 mg tablets used in clinical trials.

Noting that the proposed new tablet strengths will be used in the same target species, for the same indications and at the same posology and dosing interval as those tablet strengths already authorised, and based on the in vitro dissolution data presented, efficacy as accepted for the authorised tablet strengths may be extrapolated to the new, proposed tablet strengths. The approach of the applicant is considered acceptable, and no further data in support of efficacy of the proposed new tablet strengths is required.

The dosage table in section 3.9 of the SPC has been updated to incorporate the new, proposed tablet strengths (140 and 200 mg), along with some updates to the bodyweight bands for the existing strengths (15, 30, 45, 70 and 100 mg). The dosage table is presented in the same general format as the original table, which is considered acceptable.

The applicant has also implemented updates to two of the bodyweight ranges from the authorised table, and has provided justification for these updates.

- Concerning the first weight range in the proposed table, this has been updated from 3 – 4.9 kg, to 2.5 – 4.9 kg. The applicant states that this is needed to provide treatment with the VMP to lighter dogs for which there exists a sufficient safety margin, and notes that no minimum weight was established during the original MAA procedure for Daxocox.

  The CVMP notes that this update will result in administration of a loading dose of 12 mg/kg of enflicoxib being administered to a 2.5 kg dog; however, this is not different from that dose authorised in other weight brackets as listed (e.g. 5 – 7.5 kg) and, as such, can be accepted.

- Concerning the weight range from 11.3 – 17.5 kg in the proposed table, this replaces 2 weight ranges in the original table (11.3 – 15 kg and 15.1 – 17.5 kg). The applicant states that this update will halve the number of tablets (2 x 70 mg tablets as compared to 4 x 30 mg tablets) administered to dogs, with a still acceptable 55% 'overdose' for dogs in the lower end of this weight range.

  This update will result in administration of a loading dose of 12.39 mg/kg to an 11.3 kg dog, and a maintenance dose of 6.19 mg/kg to the same dog. These doses are slightly higher than the upper end of the dose range as published in the currently approved table (12.39 mg/kg as compared to 12 mg/kg for the loading dose, and 6.19 mg/kg as compared to 6 mg/kg for the maintenance dose). It is acknowledged that the tablets in question are indivisible and, as such, tailored dosing to all bodyweights can be challenging as a result. Based on the results of the pivotal target animal safety study presented in the original MAA in which safety of the VMP was investigated at 1X, 3X and 5X RTD, and noting that expected adverse events and warnings for safe use of the VMP have been suitably captured in the SPC, the CVMP can accept these slight increases in recommended dose.

- It is also noted that for the weight range 50.1 – 75 kg, the dose range has been slightly amended by the introduction of the new tablet strengths, specifically from 8 – 11.98 mg/kg to 7.47 – 11.18 mg/kg for the loading dose, and from 4 – 5.99 mg/kg to 3.73 – 5.59 mg/kg for the maintenance dose. The CVMP can accept this change (specifically to the lower end of the proposed dose range), noting that the table as currently authorised refers to a loading and maintenance dose (for a 4.9 kg animal) of 6.12 and 3.06 mg/kg respectively.

The CVMP considers the revised dosage table as presented by the applicant to be acceptable, and no further updates are requested.

Overall conclusions on efficacy

The applicant has not presented any data in support of efficacy of the new proposed tablet strengths and refers instead to those data already assessed in the context of the original MAA for Daxocox.

Noting that the proposed new tablet strengths will be used in the same target species, for the same indications and at the same posology and dosing interval as those tablet strengths already authorised, and based on the in vitro dissolution data presented, efficacy as accepted for the authorised tablet strengths may be extrapolated to the new, proposed tablet strengths. The approach of the applicant is considered acceptable.

The amendments proposed by the applicant to the dosing table for the currently approved tablet strengths (15, 30, 45, 70 and 100 mg) are considered acceptable.

Part 5 – Benefit-risk assessment

Introduction

Daxocox is already authorised for use in dogs for the treatment of pain and inflammation associated with osteoarthritis (or degenerative joint disease). The active substance is enflicoxib, a non-steroidal anti-inflammatory drug belonging to the coxib class and acting by selective inhibition of the enzyme cyclooxygenase 2. The product is to be administered at a first dose of 8 mg enflicoxib per kg body weight, followed by 4 mg enflicoxib per kg body weight repeated every 7 days. Daxocox tablets contain 15, 30, 45, 70 or 100 mg of enflicoxib and are presented in packs containing 4, 10, 12, 20, 24, 50 or 100 tablets.

The proposed grouped variation is to add two new tablet strengths (140 and 200 mg) and to amend the dosing table for the currently approved tablet strengths (15, 30, 45, 70 and 100 mg).

The application has been submitted in accordance with Article 62 of Regulation (EU) 2019/6.

Benefit assessment

Direct benefit

The benefit of Daxocox, containing the active substance enflicoxib, is its efficacy for the treatment of pain and inflammation associated with osteoarthritis (or degenerative joint disease) in dogs.

Additional benefits

The proposed new pharmaceutical strengths (140 mg and 200 mg) will facilitate dosing of larger dogs.

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

Safety (user, environmental, target animal) remains unaffected by this variation.

Risks for the target animal

As the proposed higher tablet strengths will be administered to the target species dogs at the same posology and dose interval as already approved, no change in risk to the target animal is identified.

Risk for the user

The most severe risk identified is accidental ingestion by a child. An appropriate warning is included in the SPC, on the outer package and the product is intended to be marketed in child-resistant packages.

Risk for the environment

Daxocox is not expected to pose a risk for the environment when used according to the SPC recommendations.

Risk management or mitigation measures

Risk management and mitigation measures remain unaffected by this variation.

Appropriate information has already been included in the SPC and other product information to inform 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.

User safety

User safety risks have been identified, mainly the risks associated with exposure in children. These risks are mitigated by the presentation of the product in a child-resistant packaging, and inclusion of suitable user safety warnings in the SPC.

Evaluation of the benefit-risk balance

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

Conclusion

Based on the original data presented, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for a variation to the terms of the marketing authorisation for Daxocox is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 2019/6), as follows: to add two new tablet strengths (140 and 200 mg) and to amend the dosing table for the currently approved tablet strengths (15, 30, 45, 70 and 100 mg).

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above mentioned medicinal product.

Changes are required in the following Annexes to the Community marketing authorisation:

I, IIIA and IIIB.

As a consequence of these variations, sections 1, 2, 3, 4, 6, and 8 of the SPC are updated. The relevant sections of the labelling and package leaflet are updated accordingly.