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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, EMA/VRA/0000246340)

INN: Enflicoxib

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

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 64 of Regulation (EU) 2019/6, the marketing authorisation holder, Ecuphar (the applicant), submitted to the European Medicines Agency (the Agency) on 15 January 2025 an application for a group of variations requiring assessment for Daxocox.

1.2. Scope of the variation

Variations requested	
G.I.7.a	Addition of a new therapeutic indication or modification of an approved one
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G.I.18	One-off alignment of the product information with version 9.0 of the QRD templates i.e. major update of the QRD templates in accordance with Regulation (EU) 2019/6, for veterinary medicinal products placed on the market in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004

The grouped variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: treatment of pain and inflammation associated with orthopaedic or soft tissue surgery and alignment of the product information with version 9.1 of the QRD template.

1.3. 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 4.

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

The product Daxocox contains enflicoxib as the active substance. Enflicoxib is a drug substance described as belonging to the anti-inflammatory and anti-rheumatic group of products known as coxibs and therefore belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs).

The product is currently authorised for oral administration to dogs for the treatment of pain and inflammation associated with osteoarthritis (or degenerative joint disease).

For the currently approved indication, the product is intended to be administered using an initial dose of 8 mg enflicoxib per kg body weight (bw) followed by repeated doses of 4 mg enflicoxib per kg body weight every 7 days. The product is intended to be administered before or with the dog's meal.

The product is available in the following tablet strengths: 15, 30, 45, 70, 100, 140 and 200 mg tablets for dogs.

The proposed grouped variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: treatment of pain and inflammation associated with orthopaedic or soft tissue surgery and alignment of the product information with version 9.1 of the QRD template. An updated summary of the product characteristics (SPC) based on QRD template version 9.1 has been provided.

2.1. Change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one (2 x G.I.7.a)

2.1.1. Safety (tolerance, user, environment)

The dose and route of administration proposed for the additional indications correspond with the posology already approved by the CVMP for the currently authorised indication for Daxocox tablets for dogs. Target animal tolerance data were submitted and evaluated in the initial marketing authorisation procedure (EMEA/V/C/005354). No new specific target animal safety studies have been submitted as part of this variation procedure; however, target animal tolerance is further demonstrated in the four efficacy studies submitted by the applicant. The safety profile observed in those studies largely reflects the known safety profile of the product.

Given that the product will be administered to the same target species, using the same route of administration and at the same posology that has already been accepted by the CVMP, no concerns in terms of user safety are considered to arise; that is, the user will not be exposed to a greater amount of the active substances or for a greater frequency than that which has been assessed for the existing indications approved for the product. No change to the impact on the environment is anticipated.

Therefore, no further assessment is deemed necessary in respect of user safety or safety for the environment and it can be concluded that the proposed modification of the indication will not present an additional risk to the one currently accepted for the user or the environment.

2.1.2. Efficacy

Dose confirmation

The currently approved posology for Daxocox is a first dose of 8 mg/kg bw followed by weekly maintenance doses of 4 mg/kg bw. This dosage was proposed at the time of the initial marketing authorisation application using PK/PD modelling combining the results of PK, toxicity and efficacy studies and was confirmed in the clinical trials. The proposed posology with the current variation for the treatment of pain and inflammation associated with orthopaedic or soft tissue surgery is 8 mg per kg body weight, administered one day before surgery is scheduled, with subsequent doses of 4 mg/kg body weight administered at 7-day intervals if required. With regard to dose determination for the proposed indications, the applicant has provided the results of a new study that was designed to analyse the available pharmacokinetic data (from two studies assessed in the context of the original marketing authorisation procedure (EMEA/V/C/005354)).

This study re-examined data from two GLP compliant studies presented in support of the initial marketing authorisation procedure. Based on the results of this study, the concentrations of enflicoxib reach the maximum level (C_{max}: 1742 ng/ml) at 2 hours post administration (T_{max}) and decrease rapidly after 24-48 hours. No Minimum Effective Concentration (MEC) has been established for enflicoxib *in vivo*; however, as previously accepted by the CVMP, enflicoxib demonstrates COX-2 inhibitory activity both *in vivo* and *in vitro*. Enflicoxib was rapidly transformed to the active metabolite E-6132. An MEC for E-6132 was established in both healthy animals (411 ng/ml) and those with osteoarthritis (700 ng/ml) during the original marketing authorisation procedure. Concentrations of E-

6132 increase steadily up to 1090 ng/ml (C_{max}) during the first 72 hours (T_{max}) and are sustained for approximately 7 days. The low boundary of the predicted 90% CI of E-6132 plasma levels reaches the MEC value of 411 ng/ml at 11 hours after Daxocox administration at 8 mg/kg bw, and the MEC value of 700 ng/ml at 26 hours post administration, remaining above those levels for a period of approximately one week.

The results of this study appear to support the proposed timing of administration of 8 mg/kg bw of enflicoxib at 24 hours prior to surgery. This dosing schedule was further investigated in the clinical trials in keeping with the Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (EMA/CVMP/EWP/1061/2001-Rev.1).

2.1.2.1. Treatment of pain and inflammation associated with orthopaedic surgery

In support of the indication concerning the treatment of pain and inflammation associated with orthopaedic surgery in dogs, the applicant has provided the results of two efficacy pilot studies and one pivotal clinical trial.

The first study is a non-pivotal pilot study designed to explore the efficacy and safety profile of Daxocox in the control of perioperative pain in dogs undergoing orthopaedic surgery. It is unclear if the study was GCP compliant, in accordance with the requirements set out in the CVMP Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (EMA/CVMP/EWP/1061/2001-Rev.1). However, as this is a pilot trial, non-GCP status can be accepted.

The study was performed with 6 clinically healthy Beagle dogs of similar age and weight that underwent experimental orthopaedic surgery (repair of cranial cruciate ligament rupture). Five dogs were treated with Daxocox while one dog was treated the control product. The control product used was an injectable solution and oral suspension containing meloxicam as the active substance. The CVMP Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drug states that the control should be authorised for the same indication in question (EMA/CVMP/EWP/1061/2001-Rev.1). It is noted that while the respective solution for injection is authorised for the alleviation of pain and inflammation following orthopaedic and soft tissue surgery, the oral suspension is not. This deviation can be accepted noting that the oral suspension contains the same active substance (meloxicam) and that this trial is a non-pivotal study.

For each dog, the study lasted 17 days, including a 7-day acclimatization period. On D-1 (approximately 24 hours before surgery), the dogs in the treatment group received a single oral dose of Daxocox at 8 mg/kg bw. In a deviation from the study protocol, the dog in the control group received meloxicam at the dose of 0.1 mg/kg bw from D-1 to D7 instead of at 0.2 mg/kg bw on D0 (at the time of surgery) and from D1 to D7 at 0.1 mg/kg bw.

A pre-anaesthesia evaluation was performed on animals the day before surgery. On D0, all dogs underwent knee surgery in the right knee. From D1 up to D10, dogs were closely examined, and signs of pain and discomfort were blindly evaluated and rated by using a Short Form of the Glasgow Composite Pain Scale (SF-GCPS). On D-1 dogs were also examined to rule out signs of pain or discomfort.

To reduce variability, all surgeries were conducted under the same preoperative, intraoperative and postoperative protocols and performed by the same surgeon, using a standardised surgical technique (Maquet Modified Procedure, MMP).

From D-1 to D7 all animals received a single oral dose of omeprazole approximately 30 minutes prior to anti-inflammatory administration (1 tablet of 20 mg/animal/day). At the end of surgery, cefovecin was administered to all animals as a single dose of 8 mg/kg bw (equivalent to 1 ml/10 kg bw).

Methadone was subcutaneously administered at t-1h (as premedication), at the dose of 0.4 mg/kg bw (equivalent to 0.04 ml/kg bw) and again at t5h, t11h and t17h post-surgery. Blood samples (1-5 ml) were collected from the jugular vein from each dog on day D-1 (acclimatisation period), D0 (pre-surgery) and D7, for haematology, biochemistry and coagulation profile.

Clinical and pain evaluation, including orthopaedic examination, was performed during acclimatisation. Pain and clinical evaluation was repeated three times daily from D1-D2 and twice daily from D3-D10. For clinical evaluation, the following parameters were also recorded: mucous membranes, temperature, heart rate (HR), respiration rate (RR). A validated pain scoring tool was used in pain evaluation (Short Form Glasgow Composite Pain Scale). Rescue analgesia was established at scores ≥ 8/24. The choice of the threshold for rescue analgesia is questioned, as the recommended analgesic intervention level for the SF-GCPS is 6/24 (Reid et al., 2007). Pain was not evaluated in the first 24 hours post-surgery, as the animals were under the effects of opioid analgesia. Therefore, the efficacy of the IVP Daxocox during the first 24 hours post-surgery could not be evaluated.

Each animal demonstrated their maximum pain and discomfort score on Day 1, with decreasing pain scores thereafter until the end of the evaluation period. Two animals were withdrawn from the study on Days 4 and 5, respectively, due to an adverse event (fracture of the leg which had been operated on), therefore further evaluations were not performed. None of the animals reached the threshold for rescue analgesia (SF-GCPS score ≥ 8/24) at any examination time point during the postoperative period. No alterations were observed on any of the blood results or parameters monitored during anaesthesia.

Regarding the blood results provided, it its noted that one dog displayed moderate, normocytic, normochromic non regenerative anaemia on complete blood count (CBC) at D-1, D0 and D7. Two dogs displayed mild normocytic, normochromic non regenerative anaemia on CBC at D-1 and D0 but not D7. These results were not deemed to be clinically significant. No alterations were observed in any of the parameters monitored during anaesthesia.

Several limitations were noted and comprise the following points: inclusion/exclusion criteria were not defined, the study population was small, with no justification for the number of animals included, only female dogs were included, which is not fully representative of the target population, the control group consisted of only one animal, the randomisation procedure used was not described. No statistical analysis was performed, but it is accepted that, based on the study design, statistical analysis would not have been possible. It is unclear whether the product was administered with or before food as described in the SPC. The concurrent administration of omeprazole may affect the assessment of gastrointestinal side effects from the test product, most notably gastrointestinal ulceration, although assessment of target animal tolerance was not the purpose of this small-scale, pilot trial. Regarding the underdosing deviation involving the animal in the control group, such a deviation has the potential to affect pain evaluation. However, given that in this study pain was not evaluated for the first 24 hours post-surgery, during which this time the dogs were receiving opioid analgesia, it is considered unlikely to affect the results of the study. The choice of the threshold for rescue analgesia is noted as being inconsistent with the recommended analgesic intervention level for the SF-GCPS, which is 6/24 (Reid et al., 2007). However, taking into account the nature of the study in question, that is a small-scale pilot trial, further comments on these limitations are not raised by the CVMP.

Taking into account the use of opioids in the immediate post-operative period, the efficacy of the IVP during the first 24 hours post-surgery could not be evaluated. Overall, this study may be considered limited in support of the newly proposed indication but sufficient as a 'proof of concept' study, that merits further investigation in the context of more comprehensive, clinical trials.

The second study was a multicentre, prospective, non-inferiority, parallel-controlled, randomized, and blinded clinical trial to evaluate the efficacy and safety of Daxocox to control pain and inflammation in dogs undergoing orthopaedic surgery compared with a reference product containing meloxicam as positive control (solution for injection and oral suspension). The study was performed broadly in line with VICH GL9 (GCP). A study protocol and statistical report have been provided. It is noted that a certificate of analysis for the test product and expiry date of the control product have not been provided. However, given that this is a non-pivotal trial and that the reference product is commercially available, no question is raised.

Thirty-two dogs (18 females and 14 males) of different breeds, ages and weights were included from four veterinary practices in Spain. All dogs were clinically healthy other than the surgical condition. The inclusion and exclusion criteria are considered appropriate and broadly in line with the CVMP Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (EMA/CVMP/EWP/1061/2001-Rev.1).

The test group comprised of 6 males and 10 females, while the control group consisted of 8 males and 8 females. The results of a basal homogeneity analysis confirmed that both treatment groups were homogeneous and balanced for all parameters and variables before treatment as well as for surgery duration. The sample size (16 animals per group) was justified based on statistical analysis. No animals were withdrawn during the study. Study animals ranged from 5 months to 12 years old, and from 4 kg to 53 kg body weight. The study animals are considered to be sufficiently representative of the intended target population as seen in veterinary practice (apart from no animals less than 4 kg). It is noted that section 3.5 of the SPC carries a warning regarding careful monitoring of treatment of dogs aged less than 6 months. The product was administered as per the proposed posology.

Regarding the use of the meloxicam-containing positive control, the CVMP Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (EMA/CVMP/EWP/1061/2001-Rev.1) states that the control product should be authorised for the same indication in question. It is noted that while the solution for injection of the control product is authorised for the alleviation of pain and inflammation following orthopaedic and soft tissue surgery, the oral suspension is not. This deviation can be accepted noting that the oral suspension contains the same active substance and that this trial is a non-pivotal study.

Daxocox was administered at a single dose of 8 mg/kg bw approximately 24 hours before the scheduled surgery time (D-1), and meloxicam was administered at 0.2 mg/kg bw SC at the time of induction (D0) and repeated orally every 24 hours at 0.1 mg/kg bw for 7 additional days (D1 to D7). For each dog, the study lasted nine days. Before inclusion, all animals were weighed and underwent thorough physical examination including blood sample analysis for routine pre-surgery haematology and biochemistry determinations to confirm the animals were suitable for inclusion. The physical examination was repeated on D0 (2 hours before surgery), D0 (8 hours after surgery), D1 and D7 post-surgery.

The anaesthesia protocol was standardised as much as possible among study sites. All animals within a single site were anaesthetised under the same protocol. The orthopaedic surgeries performed were practised and ethically acceptable in the EU, in accordance with guideline EMA/CVMP/EWP/1061/2001-Rev.1.

Pain assessments were blindly performed on D0-2h before surgery and again on D0 - 1.5h, 3h, 5h±30min, 8h±1h, D1 - 24h and D7 - 168h post-surgery. A validated pain scoring tool, Short Form of Glasgow Composite Measure Pain Scale (SF-GCPS) was used to score the level of pain in the dogs. At the same time points, the investigator also assessed pain at rest and under palpation as well as level of inflammation by means of Visual Analogue Scales (VAS). Global efficacy was assessed by the

investigators at the end of the study (D7 - 168h) and, from D1 to D7 post-surgery, the dog's wellbeing was assessed by the owner. Rescue analgesic therapy could be administered at any time during the postoperative period if the investigator considered the dog to be uncomfortable or in pain, when the SF-GCPS score was ≥6/24 or ≥5/20, or both. Reported adverse events (AEs) related or not to the products administration were recorded daily. To reduce variability, efficacy assessments were always performed by the same investigator at each site.

The use of the SF-GCPS in assessment of the primary efficacy parameters is considered appropriate and in line with guideline EMA/CVMP/EWP/1061/2001-Rev.1. Justification for the choice of this assessment tool has been provided and is considered acceptable.

Overall, it is accepted that the choice of the primary and secondary efficacy variables is considered appropriate, considering the proposed indication in this variation procedure.

The primary efficacy endpoints were treatment failure according to the need of rescue analgesic therapy and the Area Under the Curve (AUC) calculated from the SF-GCPS scores for the first 24h after surgery AUC(1.5h-24h). Eight dogs in the Daxocox group and 10 in the meloxicam group had SF-GCPS scores ≥6/24 or ≥5/20 at some time points (p=0.722). However, the attending veterinarians considered rescue analgesic therapy was not required as under their experience the dogs were comfortable, and the high scores were related to stress/anxiety behaviours rather than pain. Noting that the criteria for rescue analgesia are unambiguous, it is unclear why rescue analgesia was not implemented. That said, it is accepted that there were no statistically significant differences in the number of timepoints with SF-GCPS above the threshold for rescue between groups (p=0.722).

No statistically significant differences between groups were detected for the SF-GCPS AUC(1.5h-24h) (p=0.796), for the average SF-GCPS total scores (p=0.382), or for the SF-GCPS total scores at each time point (p>0.05). Non-inferiority of Daxocox over meloxicam was demonstrated for the SF-GCPS AUC and for the SF-GCPS average scores and at each time point. No statistically significant differences were detected between groups on the secondary efficacy endpoints pain at rest, pain under palpation and level of inflammation overall and at different time points. No statistically significant differences between groups were detected when analysing the global efficacy at the end of treatment or the owner measures of the dog's wellbeing.

Regarding statistical analysis, the non-inferiority analysis used was not defined in the study protocol, which is not in line with the CVMP Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010-Rev.1) in which it is stated that a non-inferiority margin should be specified in the study protocol. However, the applicant states that the non-inferiority margin has been used in previous published studies with similar design (Pacheco et al., 2020; Ross et al., 2022).

No safety concerns relating to administration of the IVP occurred during the course of the study. Overall, it is considered that this study is not fully in accordance with the CVMP Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (EMA/CVMP/EWP/1061/2001-Rev.1). Notwithstanding the limitations described above, the results of this study are considered sufficient to warrant confirmation of the claimed efficacy for the proposed indication in the pivotal clinical trial.

The third study was a prospective, multi-centre, randomized, masked, non-inferiority and parallel-positive controlled clinical trial, carried out to demonstrate clinical efficacy and safety of Daxocox tablets for dogs in comparison with a reference product containing the active substance firocoxib (chewable tablets) for the control of postoperative pain and inflammation associated with orthopaedic surgery. This study was well designed and conducted largely in accordance with VICH GL9 (GCP) and the CVMP Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs

(EMA/CVMP/EWP/1061/2001-Rev.1). An audit statement and a well-structured study protocol were provided. The study was conducted across 13 veterinary practices in two EU Member States, Spain and France.

A total of 216 dogs were randomized in 13 veterinary practices located in Spain and France in a 1:1 ratio: 108 in the Investigational Veterinary Product (IVP) group (Daxocox) and 108 in the Control Product (CP) group (firocoxib). The inclusion and exclusion criteria are considered appropriate and broadly in line with the aforementioned CVMP guideline. The results of a basal homogeneity analysis confirmed that both treatment groups were well balanced. The sample size was justified based on statistical analysis. The study animals are considered to be sufficiently representative of the intended target population as seen in veterinary practice. A total of 198 dogs were included in the Per Protocol population: 101 in IVP and 97 in CP groups.

The test product used was the formulation currently marketed and was administered as per the proposed posology. The selection of the control product is considered sufficiently justified, as it is an NSAID - containing veterinary medicinal product authorised in the EU, for the indication evaluated in this study.

The study duration is considered appropriate for the demonstration of efficacy. The study design is considered to be sufficiently reflective of the conditions under which Daxocox will be used in clinical practice. In line with the CVMP Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (EMA/CVMP/EWP/1061/2001-Rev.1), a pre-defined definition for "responders" was provided in the study protocol to ensure the clinical relevance of the treatment results. The guideline also states that 'Where the percentage of responders/non-responders is not the primary endpoint analysis this should be presented in addition to the primary endpoint analysis.', which was done in this case.

Daxocox was administered orally, as a single 8 mg/kg bw dose, on Day 0, approximately 24 hours before orthopaedic surgery. The control product was administered at a dose of 5 mg firocoxib/kg bw from Day 1 to Day 8, both included. To ensure blinding, dogs allocated to the CP group received a single tablet of placebo on Day 0, and dogs allocated to the IVP group received a single tablet of placebo daily from Day 1 to Day 8.

Each animal underwent a screening visit to ensure inclusion/exclusion criteria were met, an inclusion visit (Day 0), a surgery day visit (Day 1) and several follow-up visits up to Day 8. Efficacy assessments were performed by the investigator on Days 1+2h, 1+5h, 1+8h, 2, 3, 4 (+1), 6 (+1) and 8. In addition, the owner completed the Owner Response To Treatment (ORTT) score daily from Day 2 to Day 8, both included.

The Short Form of the Glasgow Composite Measure Pain Scale (SF-GCPS), a validated scoring scale for the assessment of acute pain in dogs, was used by the investigators to evaluate the animal response to treatment. Other variables, such as the inflammation assessment of the surgical wound and rescue analgesia requirement (SF-GCPS responder rate) were also evaluated by the investigators throughout the study. The owners assessed their dog's wellbeing by completing the ORTT score.

Several secondary efficacy endpoints were evaluated, such as SF-GCPS total scores, individual SF-GCPS parameters, inflammation assessment, SF-GCPS responder rate and ORTT. The SF-GCPS total score showed a similar decreasing trend through time in both treatment groups, with no statistically significant differences detected at any timepoint. When the individual SF-GCPS parameters were analysed, the distribution of scores of all six parameters was similar among animals assigned to the IVP and CP groups, with a single statistically significant difference in category D. overall (vi) on Day 6 (+1) in favour of the CP group (p=0.0037).

It is noted that the selected efficacy parameters are subjective. According to the CVMP Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (EMA/CVMP/EWP/1061/2001-Rev.1), 'if objective endpoints cannot be used, subjective assessment methods may be acceptable, provided their validity can be justified and sufficient blinding is applied. In order to reduce variability, observations should preferably be made by the same adequately trained personnel throughout the trial, and information on this and any other measures undertaken to reduce observer variation should be provided.' Appropriate measures were taken during the study to reduce variability and bias.

Adequate blinding was performed and all observations were performed by the same investigator at each site. The selected efficacy parameters are clinically relevant to the proposed indication. Similar efficacy endpoints and rating scales have been used and accepted in the assessment of other centrally authorised NSAID-containing products.

The frequency of pain assessment is considered to be adequate. The use of the SF-GCPS in pain assessment, which is validated for the assessment of acute pain in dogs, is considered appropriate and in line with guideline EMA/CVMP/EWP/1061/2001-Rev.1. As per this guideline, 'rating scales can take the form of visual analogue scales, numerical rating scales and simple descriptive scales'. Justification for the choice of this assessment tool has been provided and is considered acceptable.

The mean inflammation score values were significantly lower in the IVP group compared to the CP group on Day 1+2h, Day 1+5h and Day 1+8h (p=0.0061, 0.0416 and 0.0169, respectively). No statistically significant differences between treatment groups were detected in the overall or per timepoint SF-GCPS responder rate. The analysis of the ORTT supported the results observed in the investigators assessments, with the Quality of Analgesia scores on Day 8 being significantly more favourable for the IVP group than for the CP group (p=0.0293).

The primary efficacy endpoint was defined as the SF-GCPS total scores AUC for the first 48 hours post-surgery. Non-inferiority criterium was met in the Intention to Treat (ITT) population with a difference (IVP-CP) of -5.6608 between groups (p=0.0020 95% CI -∞, 11.7548). Similar results were observed with the PP population, where the pre-defined criterium for non-inferiority was met with a difference of -2.5760 (p=0.0078 95% CI -∞, 16.0970) with a one-sided non-inferiority t-test. The CVMP notes that in accordance with relevant guidance (EMA/CVMP/EWP/81976/2010-Rev.1) 'Generally, the confidence interval should be the one-sided 97.5% confidence interval; alternatively, the one-sided test should be at the 2.5% level'. However, when the confidence intervals were calculated with a two-sided non-inferiority test, the results were (p=0.0040, 95% CI -26.4409, 15.1194) for ITT population and (p=0.0156, 95% CI -24.8611, 19.7092) for PP population. Therefore, and based on the latter analysis, non-inferiority can be accepted by CVMP.

Regarding safety, 41 adverse events (AEs) were registered in 30 animals, with 21 AEs reported in the IVP group and 20 in the CP group. The number of dogs with AEs by treatment group was identical (15 animals). The most common AEs were vomiting and diarrhoea. The AE profile between groups is considered to be similar. The AEs seen in the test group are considered to be adequately reflected in section 3.6 of the SPC for Daxocox. The only serious adverse event (SAE) described was in an animal assigned to CP group. This dog suffered ventricular tachycardia and hypotension after anaesthetic induction. This SAE was resolved as complete recovery on the same day and investigator stablished an unlikely relationship with the study treatment.

In summary, it can be accepted that the results of this pivotal clinical trial demonstrate that Daxocox is non-inferior to the positive control used for the control of postoperative pain and inflammation associated with orthopaedic surgery in dogs. In addition, it has a safety profile comparable to that of the control product.

In conclusion, based on the data package provided (two pilot studies and one pivotal clinical trial), the CVMP can accept that Daxocox has been demonstrated to be efficacious for the treatment of pain and inflammation associated with orthopaedic surgery in dogs. Therefore, the corresponding G.I.7.a variation is considered to be approvable.

2.1.2.2. Treatment of pain and inflammation associated with soft tissue surgery

In support of the indication concerning the treatment of pain and inflammation associated with soft tissue surgery in dogs, the applicant has provided the results of one pivotal clinical trial.

The study was a prospective, multi-centre, randomized, masked, non-inferiority and parallel-positive controlled clinical trial. This study is considered pivotal in support of the proposed indication for the treatment of pain and inflammation associated with soft tissue surgery in dogs. This study was well designed and conducted largely in accordance with VICH GL9 (GCP) and the CVMP Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (EMA/CVMP/EWP/1061/2001-Rev.1). An audit statement and a well-structured study protocol were provided. The study was conducted across 24 veterinary practices in two EU Member States, Spain and France.

The objective was to demonstrate clinical efficacy and field safety of Daxocox administered orally as a single 8 mg/kg bw dose 24 hours before surgery in comparison with a reference product containing carprofen (injectable solution and chewable tablets), for the control of postoperative pain and inflammation associated with soft tissue surgery. The test product used was the formulation currently marketed, administered as per the proposed posology. The selection of the control product is considered sufficiently justified, as it is a well-established NSAID-containing veterinary medicinal product authorised in the EU for the indication evaluated in this study. The study duration is considered appropriate for the demonstration of efficacy.

The inclusion and exclusion criteria are considered appropriate and broadly in line with the aforementioned CVMP guideline. A total of 215 dogs presenting for soft tissue surgery in 24 veterinary practices located in Spain and France were randomized in a 1:1 ratio: 106 in the Investigational Veterinary Product (IVP) group (Daxocox) and 109 in the Control Product (CP) group (carprofen). The dogs were otherwise clinically healthy. The results of a basal homogeneity analysis confirmed that both treatment groups were well balanced. The sample size was justified based on statistical analysis. The study animals are considered to be sufficiently representative of the intended target population as seen in veterinary practice. A total of 198 dogs were included in the Per Protocol population: 101 in IVP and 97 in CP groups.

Daxocox was administered orally, as a single 8 mg/kg bw dose, on Day 0, approximately 24 hours before soft tissue surgery. The carprofen-containing control product was administered subcutaneously (injectable solution) at a single dose of 4 mg/kg bw on Day 1 (at the time of induction of anaesthesia), and orally (chewable tablets) at the same dose from Day 2 to Day 6, both included. To ensure blinding, dogs allocated to the CP group received a single tablet of placebo on Day 0, and dogs allocated to the IVP group received a single tablet of placebo daily from Day 2 to Day 6.

The Short Form of Glasgow Composite Measure Pain Scale (SF-GCPS), a validated scoring scale for the assessment of acute pain in dogs, was used by the investigators to evaluate the animal response to treatments. Other variables, such as the inflammation assessment of the surgical wound, rescue analgesia requirement (responder rate), were also evaluated by the investigators throughout the study. The owners assessed the dogs' wellbeing by completing the Owner's Response To Treatment (ORTT) score.

The use of the SF-GCPS in pain assessment, which is validated for the assessment of acute pain in dogs, is considered appropriate and in line with guideline EMA/CVMP/EWP/1061/2001-Rev.1.

Justification for the choice of this assessment tool has been provided and is considered acceptable. To reduce the confounding effects of sedation and anxiety, a validated sedation scale (Wagner et al., 2017) and anxiety assessment was carried out. As per the guideline, 'rating scales can take the form of visual analogue scales, numerical rating scales and simple descriptive scales'. A visual analogue scale (VAS) was used by the investigator in the assessment of the degree of inflammation of the surgical wound. A numerical rating scale (NRS) was used in the owner's response to treatment. The same owner conducted all the assessments for each dog where possible.

Each animal underwent a screening visit to ensure inclusion/exclusion criteria were met, an inclusion visit (Day 0), a surgery day visit (Day 1) and several follow-up visits up to Day 6. Efficacy assessments were performed by the investigator on Days 1+2h, 1+5h, 1+8h, 2, 3, 4 and 6. In addition, the owner completed the ORTT daily from Day 2 to Day 6, both included.

Out of the 215 dogs enrolled and included in the Safety population, 210 animals were included in the Intention to Treat (ITT) population (105 in the IVP group and 105 in the CP group) and 198 in the Per Protocol (PP) population (101 in the IVP group and 97 in the CP group). Baseline characteristics of both treatment groups were well balanced at the beginning of the study.

The primary efficacy endpoint was defined as the total SF-GCPS AUC for the first 48 hours post-surgery. Non-inferiority criterium was met in the ITT population with a difference of 2.0474 between groups (p=0.0001 95% CI -∞, 12.2844). Similar results were observed with the PP population, where the pre-defined criterium for non-inferiority was met with a difference of 4.0124 (p=0.0003 95% CI-∞, 14.0584) with a one-sided non-inferiority t-test. The CVMP notes that in accordance with relevant guidance (EMA/CVMP/EWP/81976/2010-Rev.1) 'Generally, the confidence interval should be the one-sided 97.5% confidence interval; alternatively, the one-sided test should be at the 2.5% level'. However, when the confidence intervals were calculated with a two-sided non-inferiority test, the results were (p=0.0003, 95% CI -10.1676, 14.2623) for ITT population and (p=0.0007, 95% CI -7.9755, 16.0003) for PP population. Therefore, and based on the latter analysis, non-inferiority can be accepted by CVMP. The non-inferiority margin was pre specified in the study protocol, as per the CVMP 'Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals)' (EMA/CVMP/EWP/81976/2010-Rev.1). The non-inferiority margin was justified by comparison with published data.

Several secondary efficacy endpoints were evaluated, such as SF-GCPS total scores, individual SF-GCPS parameters, inflammation assessment, ORTT and SF-GCPS responder rate. The SF-GCPS total score showed a similar decreasing trend through time in both treatment groups with significant differences being detected between groups on Day 1+2h timepoint only (p=0.0464). When the individual SF-GCPS parameters were analysed, the distribution of scores of all six parameters was similar among animals assigned to the IVP and CP groups, with minor statistically significant differences between groups. The analysis of the ORTT supported the results observed in the investigators assessments, although the quality of analgesia on Day 4 and demeanour on Day 5 were significantly better in the animals treated with Daxocox (p=0.0311 and 0.0391, respectively).

While it is noted that the selected efficacy parameters are subjective, they are clinically relevant to the proposed indication. Similar efficacy endpoints and rating scales have been used and accepted in the assessment of other centrally authorised NSAID containing products. According to the Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (EMA/CVMP/EWP/1061/2001-Rev.1) 'if objective endpoints cannot be used, subjective assessment methods may be acceptable, provided their validity can be justified and sufficient blinding is applied. In order to reduce variability, observations should preferably be made by the same adequately trained personnel throughout the trial, and information on this and any other measures undertaken to reduce observer variation should be provided'. Appropriate measures were taken during the study to reduce variability and bias.

Adequate blinding was performed and all observations were performed by the same investigator at each site. The frequency of pain assessment is considered to be adequate.

Regarding safety, no statistically significant differences were found between treatment groups in the distribution (p=0.2414), severity (p=0.1843), outcome of finished AEs (p=0.0753) and causality of AEs (p=0.1776) or the abnormal laboratory results at the end of the study (p=0.6905). No AE was considered to have a probable relation with the administration of Daxocox, while three AEs in the control group, classified as gastrointestinal disorders, were classified as probably related to product administration. In addition, none of the AEs reported in the IVP group were classified as life threatening, compared to three in the CP group. The most frequent AE observed was emesis (reported in 15 dogs), followed by diarrhoea (reported in five dogs) and one dog suffered an AE which combined emesis and diarrhoea. These adverse events are consistent with the known safety profile of Daxocox and are adequately reflected in the SPC.

Five serious adverse events (SAEs) were described during the study: one in the IVP and four SAEs in the CP group, with no statistically significant differences between groups (p=0.6351). Regarding safety, no serious AE in any group was considered to have a probable relation to treatment administration. Three deaths occurred, all in the control group, however these deaths were unlikely to be related to treatment administration.

Overall, it is accepted that this study demonstrates non-inferiority between Daxocox and the control product for the control of postoperative pain and inflammation associated with soft tissue surgery in dogs.

In conclusion, based on the data package provided (one pivotal clinical trial), the CVMP can accept that Daxocox has been demonstrated to be efficacious for the treatment of pain and inflammation associated with soft tissue surgery in dogs. Consequently, the corresponding G.I.7.a variation is considered to be approvable.

With regard to the posology for the peri-operative indications, the applicant proposes that a dose of 8 mg per kg body weight be administered one day before surgery is scheduled, with subsequent doses of 4 mg/kg body weight administered at 7-day intervals if required. It is noted that the clinical efficacy trials presented in support of these indications concerned only a single administration of the product. Notwithstanding this, given that the proposed posology is the same as that already approved by the CVMP for the osteoarthritis indication, and for which safety and efficacy have previously been demonstrated, and taking into account the intended use of the veterinary medicinal product in clinical practice, the CVMP considers the proposed posology to be acceptable. However, amendments to the proposed wording in Section 3.9 of the SPC were requested by the CVMP, to reflect that the decision to administer further doses of the VMP for the peri-operative indication should be based on the clinical judgement of the veterinarian. These amendments were accepted by the applicant.

2.2. Alignment of the product information with version 9.1 of the QRD template (G.I.18)

This grouped variation includes a variation to align the product information with version 9.1 of the QRD templates. The information has been largely transcribed directly from the relevant sections of the previously approved product information to the relevant sections of the newly proposed product information presented with this application. However, additional amendments to the product information were considered necessary and the applicant accepted these amendments. The revised product information is considered acceptable by the CVMP.

3. Benefit-risk assessment of the proposed change

Daxocox is authorised as tablets 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.

The proposed variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: treatment of pain and inflammation associated with orthopaedic or soft tissue surgery and alignment of the product information with version 9.1 of the QRD template.

3.1. Benefit assessment

Direct therapeutic benefit

As this is a variation to introduce additional indications to existing presentations of the product Daxocox tablets for dogs, the benefit will arise from the inclusion of these indications. The indications for the treatment of pain and inflammation associated with orthopaedic and soft tissue surgery in dogs are considered as being of benefit for the user/prescriber and patient. The proposed direct therapeutic benefit of Daxocox is its efficacy in the treatment of post-operative pain and inflammation associated with orthopaedic and soft tissue surgery in dogs, which was established in a number of well-designed clinical trials conducted in accordance with GCP.

Additional benefits

The additional benefit anticipated with the proposed indications is the ease of use, given that the posology differs to that of existing NSAID-containing veterinary medicinal products authorised for these indications, which require daily dosing. The one-off dosing schedule may improve treatment compliance.

3.2. Risk assessment

As this is a variation to introduce additional indications to existing presentations of the product Daxocox tablets for dogs, the risk assessment focuses on potential risks arising from the introduction of the proposed indications. As the product will be administered to the same target species at the same dose rate as already approved for existing indications, no new risk is considered to arise in terms of user safety or for the environment.

Regarding target animal tolerance, the data provided as part of the clinical trials demonstrate that when used in accordance with SPC recommendations, the veterinary medicinal product does not present an unacceptable risk to the target animal. The adverse events recorded in these studies are consistent with the known safety profile of Daxocox and are adequately reflected in the SPC.

Quality:

Quality remains unaffected by this variation.

Safety:

Risks for the target animal:

Administration of Daxocox to dogs in accordance with SPC recommendations is generally well tolerated. The main reported adverse events included vomiting and diarrhoea, which are already reflected in the product information.

Risk for the user:

The CVMP previously concluded that user safety for this product is acceptable when used according to the SPC recommendations. The frequency of treatment does not increase due to the addition of these indications. Therefore, no additional risk for the user arises.

The most severe risk is accidental ingestion by a child. An appropriate warning is included in the SPC and the product is 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.

3.3. 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 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. It is considered that user exposure will not be affected by the proposed indications.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality, user safety, environmental safety, target animal safety.

The product has been shown to be efficacious for the treatment of pain and inflammation associated with orthopaedic or soft tissue surgery in dogs.

The product 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 benefit-risk balance remains unchanged.

4. Conclusion

Based on the original and complementary data presented on efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Daxocox can be approved, since the data satisfy the requirements as set out in the legislation (Regulation (EU) 2019/6), as follows: change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: treatment of pain and inflammation

associated with orthopaedic or soft tissue surgery and alignment of the product information with version 9.1 of the QRD template.

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, II, IIIA and IIIB.

As a consequence of these variations, all sections of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.