18 May 2011
EMA/922888/2011

EPAR type II variation for Previcox

International Non-proprietary Name: Firocoxib 57 mg and 227 mg chewable tablets

Procedure No. EMEA/V/C/082/II/028

EU/2/04/045/001-006

Scope:

Type II – to authorise an additional indication in the target species (dog) for Previcox chewable tablets for dogs for both strengths (57 mg and 227 mg): dental surgery when administered for up to 3 days at the same dose as that used for the existing authorised indications.

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1. Background information on the variation

1.1. Submission of the variation application

Pursuant to Article 16 of Commission Regulation (EC) No. 1234/2008, the Marketing Authorisation Holder, Merial S.A.S., submitted to the Agency on 8 November 2010 an application for a Type II variation for Previcox.

1.1.1. Scope of the variation

Previous	Current
4.2 Indications for use, specifying the target species For the relief of pain and inflammation associated with osteoarthritis in dogs. For the relief of post-operative pain and inflammation associated with soft-tissue and orthopaedic surgery in dogs.	**4.2 Indications for use, specifying the target species** For the relief of pain and inflammation associated with osteoarthritis in dogs. For the relief of post-operative pain and inflammation associated with soft-tissue, orthopaedic and dental surgery in dogs.

2. Scientific discussion

Previcox was indicated for use in dogs for the relief of post-operative pain and inflammation associated with soft-tissue and orthopaedic surgery. The dose used in the study investigating the efficacy of the product for the control of pain and inflammation in dogs associated with dental surgery was the same as that was approved for soft-tissue and orthopaedic surgery; namely, 5 mg/kg once daily for up to 3 days commencing approximately 2 hours before surgery.

No new preclinical studies or specific target animal safety studies have been conducted by the applicant in the context of this variation application.

Given that no change to the posology or target species was proposed, no new user safety assessment or environmental risk assessment has been provided.

Given that the product was already approved for the relief of post-operative pain and inflammation following soft-tissue and orthopaedic surgery at a dose of 5 mg/kg for 3 days, the absence of dose determination/dose confirmation studies in respect of the newly proposed indication can be accepted. Furthermore, the safety of the product when administered in accordance with the proposed posology for the new indication has already been assessed and approved during previous applications (for example, EMEA/V/C/082/II/014).

In conclusion, no further assessment was deemed necessary in respect of target animal tolerance, user safety or safety for the environment.

The provided results confirm the clinical efficacy of chewable tablets administered orally before and after dental surgery in controlling pain and inflammation associated with dental surgery (maxillary tooth extraction).

This was a well-designed, GCP compliant single site, double blinded, negative control clinical study. The study was conducted in Australia and the product used in this study was identical to that commercialised in the EU. The fact that the study was conducted in Australia as opposed to within the EU was not considered to be a deficiency: it is not expected that there will be any differences between

the territories with regard to the condition under investigation or the methodologies used that the findings of the study can be considered relevant in an EU context.

The age, weight, sex and breeds of dogs included in the study were considered to be representative of the general canine population and in line with the target animal population for which the product is indicated.

Included animals were dogs necessitating a maxillary teeth/tooth extraction. Whilst there may be other dental procedures that might be expected to result in pain and/or inflammation post-surgery, the choice of dental procedure included in the study (canine maxillary tooth extraction) can be accepted as being representative of a painful dental surgical procedure undertaken in clinical practice. Exclusion criteria included prior surgery (within 30 days), prior treatment (within 14 days) with anti-inflammatory or analgesic drugs, pregnant bitches and animals aged less than 10 weeks of age or weighing less than 3 kg.

All animals received pre-operative morphine and one additional dose post-operatively, immediately prior to extubation. Administration of morphine to both the sham dosed group and the Previcox treated group was not expected to have introduced bias nor affect the outcome of the study. Furthermore, the protocol permitted analgesia intervention when the investigator deemed additional analgesia was necessary.

The applicant has assessed the primary efficacy variable (pain) using a VAS scoring system. Whilst a multidimensional pain rating scale (such as the GCPS) has not been used, it can be accepted that the applicant has chosen an acceptable method for the assessment of pain and was considered to be in line with the recommendation included in the CVMP Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (EMEA/CVMP/237/01-Final). In addition, the outcome of the study confirmed the appropriateness of the method in that it was shown to be sufficiently sensitive to detect differences between the treatment and placebo groups.

The secondary efficacy variable was success/failure with failure defined as a need to administer rescue medication (additional analgesia).

It was noted that at enrolment, animals were paired (where possible) according to the existing dental pathology and the expected severity of the intended dental procedure (for example, number of teeth to be extracted). Whilst VAS scores for the study animals were established prior to surgery, it would appear that the observed values (prior to surgery) were not considered when pairing animals at enrolment. However, it can be accepted that pre-surgical pain (VAS scores measured Day-3 to 0) was not likely to be an accurate indicator of post-surgical pain (which will be influenced primarily by the extent of the surgical procedure).

Overall, it was accepted that the applicant has taken appropriate measures (random allocation to study groups, replicates of animals with similar dental pathology, double blinding, single study centre and same investigator assessing pain in the same animal) to reduce variability/bias in the study.

Statistically significant lower Visual Analogue Scale (VAS) scores were observed in the Previcox treated animals as early as 90 minutes post extubation in addition to the effects of morphine. Maximal difference in VAS scores was observed at 5 hours post extubation which would be the time point at which the effects of morphine administration would be expected to disappear (approximately 3 to 4 hours duration post-administration).

It was noted that no dogs (including those in the negative control group) were judged by the study investigator to require rescue medication. However, the administration of morphine prior to surgery and at extubation in the negative control group was expected to provide pain relief during the most painful period of the procedure.

The findings of the study indicated that the product was well tolerated in the study animals with the product administered in accordance with label recommendations for three days. The incidence of adverse effects was low overall and there was no statistically significant difference between the treated group and the untreated control group in respect of the broad range of physical, haematological, urological or biochemical parameters measured. It was noted that adverse effects that may reflect oral pain (anxiety, oral discomfort, tachypnoea, vocalisation and inappetence) were more common in the sham dosed group. The adverse effects recorded were not considered by the applicant to be treatment related.

In this study, only two animals (both administered Previcox) were observed with adverse events related to the gastrointestinal tract (vomiting). For both dogs, vomiting occurred following the final (third) treatment. The CVMP was of the opinion that these adverse effects should be considered possibly treatment-related. However, it was accepted that the vomiting was on a single occasion and can be classed as mild.

Whilst it might be considered that the oral administration of tablets to dogs having recently undergone maxillary canine tooth extraction may be difficult, it would appear that no difficulties were experienced in administering the product in this study.

Overall conclusion

Based upon the results of the study provided, it can be concluded that the applicant has satisfactorily demonstrated that the administration of the product (Previcox) at a dose rate of 5 mg/kg on three occasions at 24 hour intervals, commencing approximately 2 hours before surgery, is effective in reducing post-operative pain following dental surgery (extraction of maxillary canine teeth) as measured using a visual analogue scale.

3. Benefit-risk assessment

3.1. Benefit assessment

Direct benefits arise from the relief of inflammation and pain following tooth extraction.

3.2. Risk assessment

The proposed indication for the relief of post-operative pain and inflammation associated with dental surgery in dogs was related to the administration of the product at the same posology as that which was approved. It can therefore be concluded that no new risk should arise from the introduction of a claim in respect of dental surgery.
No change to the impact on the environment was envisaged.

3.3. Evaluation of the benefit risk balance

Given that it is not expected that any new risk will result from the inclusion of the proposed additional indication, it can be accepted that there should be an increased benefit from the use of the product before and following dental surgery in dogs. Benefits arise in terms of control of pain and inflammation following dental surgery.

4. Conclusion

The CVMP considered that this variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

5. Changes to the community marketing authorisation

Changes were required in the following annexes of the Community Marketing Authorisation:

- Annex I, II and IIIB.