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EMA/674662/2011

EPAR type II variation for Metacam

International Non-proprietary Name: Meloxicam

Procedure No. EMEA/V/C/033/II/084

EU/2/97/004/026, 33-34

Scope:

Type II – Addition of indication for cats

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1. Background information on the variation

1.1. Submission of the variation application

On 20 November 2009 the European Commission updated the marketing authorisation for veterinary medicinal product Metacam amending 0.5 mg/ml oral suspension for cats indicated for alleviation of inflammation and pain in chronic musculo-skeletal disorders. On 2 June 2010 the European Commission updated the marketing authorisation for veterinary medicinal product Metacam 0.5 mg/ml oral suspension for cats amending the indication by "Alleviation of mild to moderate post-operative pain and inflammation following surgical procedures in cats, e.g. orthopaedic and soft tissue surgery".

Pursuant to Article 16 of Commission Regulation (EC) No. 1234/2008, the Marketing Authorisation Holder, Boehringer Ingelheim Vetmedica GmbH, submitted to the European Medicines Agency on 2 September 2010 an application for a Type II variation for Metacam.

1.1.1. Scope of the variation

Addition of indication: "Alleviation of pain and inflammation in acute musculo-skeletal disorders in cats" as well as additional information on the posology regarding the amounts to be administered and duration of treatment reflected in the product literature.

Summary of Product Characteristics (SPC) changes:

Previous	Current
4.2 Alleviation of mild to moderate post-operative pain and inflammation following surgical procedures in cats, e.g. orthopaedic and soft tissue surgery. Alleviation of pain and inflammation in chronic musculo-skeletal disorders in cats.	4.2 Alleviation of mild to moderate post-operative pain and inflammation following surgical procedures in cats, e.g. orthopaedic and soft tissue surgery. Alleviation of pain and inflammation in **acute and** chronic musculo-skeletal disorders in cats.
4.9 <u>Post-operative pain and inflammation following surgical procedures</u> After initial treatment with Metacam 2 mg/ml solution for injection for cats, continue treatment 24 hours later with Metacam 0.5 mg/ml oral suspension for cats at a dosage of 0.05 mg meloxicam/kg body weight. The oral follow-up dose may be administered once daily (at 24-hour intervals) for up to four days. <u>Chronic musculo-skeletal disorders:</u> Initial treatment is a single oral dose of 0.1 mg meloxicam/kg body weight on the first day. Treatment is to be continued once daily by oral administration (at 24-hour intervals) at a maintenance dose of 0.05 mg meloxicam/kg	4.9 <u>Post-operative pain and inflammation following surgical procedures</u> After initial treatment with Metacam 2 mg/ml solution for injection for cats, continue treatment 24 hours later with Metacam 0.5 mg/ml oral suspension for cats at a dosage of 0.05 mg meloxicam/kg body weight. The oral follow-up dose may be administered once daily (at 24-hour intervals) for up to four days. **<u>Acute musculo-skeletal disorders:</u>** **Initial treatment is a single oral dose of 0.2 mg meloxicam/kg body weight on the first day. Treatment is to be continued once daily by oral administration (at 24-hour intervals) at a dose of 0.05 mg meloxicam/kg body**

body weight. A clinical response is normally seen within 7 days. Treatment should be discontinued after 14 days at the latest if no clinical improvement is apparent.	**weight for as long as acute pain and inflammation persist.** Chronic musculo-skeletal disorders: Initial treatment is a single oral dose of 0.1 mg meloxicam/kg body weight on the first day. Treatment is to be continued once daily by oral administration (at 24-hour intervals) at a maintenance dose of 0.05 mg meloxicam/kg body weight. A clinical response is normally seen within 7 days. Treatment should be discontinued after 14 days at the latest if no clinical improvement is apparent.

2. Scientific discussion

Target animal tolerance

The applicant referred to target animal tolerance data provided in relation to previous applications for treatment of cats with 0.5 mg/ml oral suspension. Since the dosing strategy suggested for the proposed indication is the same as that authorised for treatment of post-operative pain and inflammation following surgical procedures besides the duration of treatment, this approach is acceptable. Safety data is reported from the clinical study submitted in support of the current application (see under "Clinical studies"). No additional safety information would be needed.

Dose determination/dose justification

No new data was presented to justify the dose, but the applicant referred to studies submitted in support of the previously accepted indications concerning post-operative pain and chronic musculo-skeletal disorders, to justify the proposed dose for the current new indication.

From two experimental studies (Carroll et al, Journal of Veterinary Pharmacology and Therapeutics, 2008; Carroll et al, Veterinary Anaesthesia and Analgesia, 2011) in which arthritis was induced by injection sodium urate the applicant concluded that 0.05 mg/kg is effective. From this information and clinical data submitted to support the previous indication the applicant further concluded that an initial loading dose of 0.1 mg/kg oral suspension followed by once daily treatment with 0.05 mg/kg is effective for the treatment of chronic musculo-skeletal disorders. For the recently authorised indication post-operative pain the applicant came to the conclusion, on basis of clinical data and data on simulated plasma concentration-time profiles of meloxicam using either a 0.1 mg/kg or a 0.2 mg/kg loading dose followed by 0.05 mg/kg maintenance dose, that 0.2 mg/kg body weight (solution for injection) was an appropriate loading dose which was effective in alleviating mild to moderate post-operative pain when combined with follow-up treatment at the dose 0.05 mg/kg body weight.

The originally proposed loading dose (0.1 mg/kg body weight) was questioned by CVMP based on the fact that previously submitted data demonstrated that 0.2 mg/kg body weight as loading dose is needed to alleviate mild to moderate pain in connection to soft tissue and orthopaedic surgery. It was agreed, in consideration of all data on dose determination available for cats that 0.2 mg/kg body weight as loading dose would ensure / be more appropriate to alleviate pain of any magnitude according to the new proposed indication.

Clinical trials

To support efficacy and safety the applicant submitted data from a clinical field study, where cats suffering acute pain due to various kinds of musculo-skeletal disorders were treated with Metacam 0.5 mg/ml oral suspension for 5 days. The results from the pivotal clinical field study submitted to support the current application suggested that meloxicam at an initial loading dose of 0.1 mg/kg oral suspension followed by once daily treatment with 0.05 mg/kg is non-inferior to ketoprofen tablets at 1 mg/kg once daily for treatment of painful acute locomotor disorders (Morton et al., Journal of Feline Medicine and Surgery, 2011), according to the pre-set limit 1 score point on a 12 graded scale reflecting lameness and pain (summary score). However, concerns were raised with regard to internal validity of the non inferiority study. Due to these deficiencies the study was regarded as supportive. Nevertheless, CVMP came to the conclusion that sufficient support for the new indication is available taking into account all experimental and clinical data provided in connection to this and previous applications for chronic as well as acute pain and inflammation in cats. From this bulk of data a loading dose of 0.2 mg/kg body weight followed by a maintenance dose of 0.05 mg/kg body weight as long as needed according to clinical condition, was regarded sufficiently supported for the alleviation of inflammation and pain in acute musculo-skeletal disorders.

3. Benefit-risk assessment

3.1. Benefit assessment

A benefit of treatment is the alleviation of pain and inflammation in cats suffering from acute musculo-skeletal disorder.

An indirect benefit is that the oral solution allows a precise dosing and good acceptability due to its good palatability.

3.2. Risk assessment

Treatment with meloxicam is connected to well known risks for NSAID-associated adverse events, mainly related to gastrointestinal and renal integrity. Appropriate risk mitigation measures are presented in the SPC. The new indication will not bring any change in exposure as compared to previously authorised use in cats and thus the risk is expected to be similar.

3.3. Evaluation of the benefit risk balance

A benefit is to alleviate pain and inflammation in cats suffering from acute musculo-skeletal disorder. Although efficacy and the proposed dosing strategy was not fully supported through the new data presented in this application, the indication and a slightly revised dosing regimen is regarded to be sufficiently supported through clinical and experimental data on cats previously presented to CVMP. The formulation provides precise dosing and good palatability and thus good acceptability which is beneficial from both efficacy and safety perspectives. The risk connected to treatment according to the new proposed indication is regarded acceptably low provided the risk mitigation measures presented in the current SPC are followed. The variation is not considered to have any impact on the environment.

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.

No change to the impact on the environment is envisaged.

5. Changes to the community marketing authorisation

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

- Annexes I and IIIB.