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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a grouped variation requiring assessment for Metacam (EMEA/V/C/000033/VRA/0151/G)

INN: meloxicam

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, Boehringer Ingelheim Vetmedica GmbH (the applicant), submitted to the European Medicines Agency (the Agency) on 6 November 2023 an application for a group of variations requiring assessment for Metacam.

1.2. Scope of the variation

Variations requested	
G.I.7.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one
G.I.4	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.

The grouped variation is to modify the indication for use in cats for Metacam 5 mg/ml solution for injection for dogs and cats and to amend the product information for Metacam 5 mg/ml solution for injection for dogs and cats, Metacam 2 mg/ml solution for injection for cats, and Metacam 0.5 mg/ml oral suspension for cats and guinea pigs with regard to the follow-up oral treatment after initial injectable administration in cats. In addition, the applicant takes the opportunity to make editorial changes to the labelling for Metacam 1.5 mg/ml oral suspension for dogs and to correct translation errors in the product information.

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.

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

Metacam 5 mg/ml solution for injection for dogs and cats is currently approved for use in cats as a single subcutaneous injection at a dose of 0.3 mg meloxicam/kg body weight (bw). Metacam 2 mg/ml solution for injection for cats is approved for use in cats as a single subcutaneous injection at doses of 0.2 mg and 0.3 mg meloxicam/kg bw. The dose of 0.2 mg meloxicam/kg bw may be followed 24 hours later by administration of Metacam 0.5 mg/ml oral suspension for cats and guinea pigs at a dose of 0.05 mg meloxicam/kg body weight. The oral follow-up treatment may be administered for up to a total of four doses at 24-hour intervals. The dose of 0.3 mg meloxicam/kg bw should not be followed-up by oral treatment with Metacam 0.5 mg/ml oral suspension.

The applicant applied for a grouped variation to harmonise the indication for use and posology in cats for Metacam 5 mg/ml solution for injection for dogs and cats with Metacam 2 mg/ml solution for injection for cats. Minor amendments to the product information for Metacam 0.5 mg/ml oral suspension for cats and guinea pigs are also proposed to reflect the proposed harmonisation.

2.1. Modification of the indication for use in cats for Metacam 5 mg/ml solution for injection for dogs and cats

With the current variation application, the following amendment to the indication for use in cats for Metacam 5 mg/ml solution for injection for dogs and cats is proposed (deletions in strikethrough, additions underlined):

"Alleviation of mild to moderate ~~Reduction of~~ post-operative pain and inflammation following surgical procedures in cats, e.g. orthopaedic and ~~after ovariohysterectomy and minor~~ soft tissue surgery."

No new studies have been conducted in support of this variation. However, the applicant makes reference to the studies previously conducted and submitted in support of the same indication for use and posology for Metacam 2 mg/ml solution for injection for cats, which were performed with Metacam 5 mg/ml solution for injection for dogs and cats and were assessed by the CVMP in the context of procedure EMEA/V/C/033/X/074.

In this previous procedure, a new dosing regimen was proposed in cats – a lower dose (0.2 mg/kg bw) of Metacam 2 mg/ml solution for injection, followed by 0.05 mg/kg bw of Metacam 0.5 mg/ml oral suspension daily for maximum 4 days. The support for the lower dosing strategy was dependent on a non-inferiority study where cats subjected to fracture surgery were provided the new proposed dosing strategy (5 mg/ml solution for injection, 0.2 mg/kg bw before surgery followed by 0.5 mg/ml oral suspension, 0.05 mg/kg bw daily for maximum 4 days). According to the results presented, this treatment strategy is non-inferior to the positive comparator 6 mg tolfenamic acid tablet provided twice daily (1.5-3 mg/kg bw). However, this study was not regarded as fully conclusive. The marketing authorisation holder responded to these concerns by providing results from a placebo-controlled study including preemptive butorphanol and butorphanol rescue treatment in both treatment groups where the pain relieving effect of Metacam was explored after orthopaedic surgery. The results of this study were considered to provide sufficient additional support for efficacy with regard to treatment of post-operative pain following orthopaedic surgery at the proposed dosing regimen. It was, however, also concluded that Metacam treatment alone may not be sufficient in case of severe pain and a restriction of the indication to reflect this fact was considered necessary.

The proposed amendment of the indication for use in cats for Metacam 5 mg/ml solution for injection for dogs and cats is fully in line with the already approved indication for Metacam 2 mg/ml solution for injection for cats. It is therefore considered acceptable to amend the indication for use and posology in cats for Metacam 5 mg/ml solution for injection for dogs and cats as proposed by the applicant.

2.2. Amendments to the product information regarding the follow-up oral treatment after initial injectable administration in cats

Metacam 5 mg/ml solution for injection for dogs and cats

The following amendments are proposed (deletions in strikethrough, additions underlined):

SPC section 4.5

"For post-operative pain and inflammation following surgical procedures in cats:
In case additional pain relief is required, multimodal pain therapy should be considered."

This sentence is included in the current SPC of Metacam 2 mg/ml solution for injection for cats, to reflect that Metacam treatment alone may not be sufficient to reduce pain to an acceptable level. It is considered appropriate to also include this statement in the SPC of Metacam 5 mg/ml solution for injection for dogs and cats.

SPC section 4.9

"Cats:

Reduction of post-operative pain and inflammation when administration of meloxicam is to be continued as an oral follow-up therapy:
Single subcutaneous injection at a dosage of 0.2 mg meloxicam/kg body weight (i.e. 0.04 ml/kg body weight) before surgery, for example at the time of induction of anaesthesia. To continue treatment for up to five days, this initial dose may be followed 24 hours later by administration of 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 for up to a total of four doses at 24 hours intervals.

Reduction of post-operative pain and inflammation where no oral follow-up treatment is possible e.g. feral cats:
Single subcutaneous injection at a dosage of 0.3 mg meloxicam/kg body weight (i.e. 0.06 ml/kg body weight) before surgery, for example at the time of induction of anaesthesia.
In this case do not use oral follow up treatment."

This section has been aligned with the new/amended text in the SPC for Metacam 2 mg/ml solution for injection for cats. The amendments are acceptable.

Metacam 2 mg/ml solution for injection for cats

The following amendments are proposed (deletions in strikethrough, additions underlined):

SPC section 4.9

"Reduction of post-operative pain and inflammation when administration of meloxicam is to be continued as an oral follow-up therapy:
Single subcutaneous injection at a dosage of 0.2 mg meloxicam/kg body weight (i.e. 0.1 ml/kg body weight) before surgery, for example at the time of induction of anaesthesia.
To continue treatment for up to five days, this initial dose may be followed 24 hours later by administration of 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 for up to a total of four doses at 24 hour intervals.

Reduction of post-operative pain and inflammation where no oral follow-up treatment is possible e.g. feral cats:
Single subcutaneous injection at a dosage of 0.3 mg meloxicam/kg body weight (i.e. 0.15 ml/kg body weight) before surgery, for example at the time of induction of anaesthesia. ~~has also been shown to be safe and efficacious for the reduction of post-operative pain and inflammation.~~
~~This treatment can be considered in cats undergoing surgery where no oral follow-up treatment is possible e.g. feral cats.~~ In this case do not use oral follow up treatment."

This section has been amended to include headings to clearly separate the two different dosage regimens. This is acceptable.

Metacam 0.5 mg/ml oral suspension for cats and guinea pigs

The following amendments are proposed (deletions in strikethrough, additions underlined):

SPC section 4.8

"In cats, pre-treatment with anti-inflammatory substances other than Metacam ~~2 mg/ml~~ solution for injection ~~for cats~~ at a single dose of 0.2 mg/kg may result in additional or increased adverse effects and accordingly a treatment-free period with such veterinary medicinal products should be observed for at least 24 hours before commencement of treatment. The treatment-free period, however, should take into account the pharmacological properties of the products used previously."

SPC section 4.9

"Cats:
Dosage
Post-operative pain and inflammation following surgical procedures:
After initial treatment with Metacam ~~2 mg/ml~~ solution for injection with a starting dosage of 0.2 mg/kg ~~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."

The amendments of SPC sections 4.8 and 4.9 are proposed with the purpose of not restricting the initial injectable treatment to only the 2 mg/ml solution. The amendments are acceptable.

In conclusion, the changes proposed by the applicant to the product information for Metacam 5 mg/ml solution for injection for dogs and cats, Metacam 2 mg/ml solution for injection for cats, and Metacam 0.5 mg/ml oral suspension for cats and guinea pigs with regard to the follow-up oral treatment after initial injectable administration in cats can be accepted.

3. Benefit-risk assessment of the proposed change

Metacam is authorised for various therapeutic indications in different target species and is available as several pharmaceutical forms and strengths:

- 5 mg/ml solution for injection for cattle and pigs;
- 20 mg/ml solution for injection for cattle, pigs and horses;
- 40 mg/ml solution for injection for cattle and horses;
- 15 mg/ml oral suspension for horses;
- 15 mg/ml oral suspension for pigs;
- 0.5 mg/ml oral suspension for dogs;
- 1.5 mg/ml oral suspension for dogs;
- 1 mg and 2.5 mg chewable tablets for dogs;
- *5 mg/ml solution for injection for dogs and cats;*
- *2 mg/ml solution for injection for cats;*
- *0.5 mg/ml oral suspension for cats and guinea pigs.*

The active substance is meloxicam, a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class.

The proposed variation is to modify the indication for use in cats for Metacam 5 mg/ml solution for injection for dogs and cats and to amend the product information for Metacam 5 mg/ml solution for injection for dogs and cats, Metacam 2 mg/ml solution for injection for cats, and Metacam 0.5 mg/ml oral suspension for cats and guinea pigs with regard to the follow-up oral treatment after initial injectable administration in cats. In addition, the applicant takes the opportunity to make editorial changes to the labelling for Metacam 1.5 mg/ml oral suspension for dogs and to correct translation errors in the product information.

3.1. Benefit assessment

Direct therapeutic benefit

The amended indication and addition of a new treatment posology for Metacam 5 mg/ml solution for injection for dogs and cats will increase the available treatment options for the alleviation of mild to moderate post-operative pain and inflammation following surgical procedures in cats, e.g. orthopaedic and soft tissue surgery.

3.2. Risk assessment

Safety:

The variation is considered to reduce the risk that cats are erroneously treated with Metacam 5 mg/ml solution for injection for dogs and cats at the dose of 0.3 mg/kg bw followed by a dose of 0.05 mg/kg bw once daily of Metacam 0.5 mg/ml oral suspension for cats and guinea pigs.

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

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 and environmental safety.

Metacam 5 mg/ml solution for injection for dogs and cats has been shown to be efficacious for the alleviation of mild to moderate post-operative pain and inflammation following surgical procedures in cats, e.g. orthopaedic and soft tissue surgery. The variation is considered to reduce the risk that cats are erroneously treated with Metacam 5 mg/ml solution for injection for dogs and cats at the dose of 0.3 mg/kg bw followed by a dose of 0.05 mg/kg bw once daily of Metacam 0.5 mg/ml oral suspension for cats and guinea pigs.

Based on the data presented, the overall benefit-risk is deemed positive.

4. Conclusion

Based on the original data presented on safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Metacam can be approved, since the data satisfy the requirements as set out in the legislation (Regulation (EU) 2019/6), as follows: to modify the indication for use in cats for Metacam 5 mg/ml solution for injection for dogs and cats and to amend the product information for Metacam 5 mg/ml solution for injection for dogs and cats, Metacam 2 mg/ml solution for injection for cats, and Metacam 0.5 mg/ml oral suspension for cats and guinea pigs with regard to the follow-up oral treatment after initial injectable administration in cats. In addition, the applicant takes the opportunity to make editorial changes to the labelling for Metacam 1.5 mg/ml oral suspension for dogs and to correct translation errors in the product information.

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 4.2, 4.5, 4.8 and 4.9 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.