15 February 2018
EMA/111961/2018
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for a type II variation for Metacam (EMEA/V/C/000033/II/0127)

International non-proprietary name: meloxicam

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

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1. Background information on the variation

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Boehringer Ingelheim Vetmedica GmbH (the applicant), submitted to the European Medicines Agency (the Agency) an application for a type II variation for Metacam.

On 20 September 2016 the CVMP agreed that the data requirements specified in the appropriate CVMP guidelines on "Minor-Use-Minor-Species" (MUMS) are applicable when assessing the application.

1.2. Scope of the variation

Variation requested		**Type**
C.II.1	Variations concerning a change to or addition of a non-food producing target species	II

The variation is to register an additional non-food producing target species, the guinea pig, for treatment with Metacam 0.5 mg/ml oral suspension.

Current	**Proposed**
ANNEX I **SUMMARY OF PRODUCT CHARACTERISTICS**	**ANNEX I** **SUMMARY OF PRODUCT CHARACTERISTICS**
Metacam 0.5 mg/ml oral suspension for cats	Metacam 0.5 mg/ml oral suspension for cats and guinea pigs
4. CLINICAL PARTICULARS **4.1 Target species** Cats	**4. CLINICAL PARTICULARS** **4.1 Target species** Cats and guinea pigs
4.2 Indications for use, specifying the target species	**4.2 Indications for use, specifying the target species** Guinea pigs: For the relief of post-operative pain associated with soft tissue surgery such as castration.
4.3 Contraindications	**4.3 Contraindications** Do not use in guinea pigs less than 4 weeks of age.
4.5 Special precautions for use **Special precautions for use in animals**	**4.5 Special precautions for use** **Special precautions for use in animals** ….Post-operative pain and inflammation following surgical procedures in cats and guinea pigs**:** In case additional pain relief is required, multimodal pain therapy should be considered. Chronic musculoskeletal disorders in cats: …
4.9 Amounts to be administered and administration route	**4.9 Amounts to be administered and administration route**

	Cats: Dosage…. ... Guinea pigs: Dosage Post-operative pain associated with soft tissue surgery: Initial treatment is a single oral dose of 0.2 mg meloxicam/kg body weight on day 1 (pre-surgery). Treatment is to be continued once daily by oral administration (at 24-hours intervals) at a dose of 0.1 mg meloxicam/kg body weight on day 2 to day 3 (post-surgery). Route and method of administration The suspension can be given using the drop dispenser of the bottle. Dosing procedure using the drop dispenser of the bottle: Dose of 0.2 mg meloxicam/kg body weight: 12 drops /kg body weight Dose of 0.1 mg meloxicam/kg body weight: 6 drops /kg body weight Alternatively a commercially available standard 1 ml syringe graduated with ml scale and 0.01 ml increments can be used for oral administration. Dosing procedure using a standard 1 ml syringe with ml scale and 0.01 ml increments: For initiation of the treatment the initial dose volume of Metacam 0.5 mg/ml oral suspension corresponding to 0.2 mg meloxicam/kg body weight (i.e. 0.4 ml/kg body weight) will be required. Treatment is to be continued with a maintenance volume equivalent to 0.1 mg meloxicam/kg body weight (i.e. 0.2 ml/kg body weight) for two days. Do not use the cat syringe with the kg-body weight scale and the cat pictogram for guinea pigs
5.2 Pharmacokinetic particulars	**5.2 Pharmacokinetic particulars** Cats: Absorption….

The changes will be reflected accordingly in Annex II and III.

1.3. Scientific advice

Not applicable.

1.4. MUMS/limited market status

The applicant requested classification of this application as MUMS/limited market by the CVMP, and the Committee confirmed in October 2016 that, where appropriate, the data requirements in the relevant CVMP guideline(s) on minor use minor species (MUMS) would be applied when assessing the application. MUMS/limited market status was granted as guinea pigs are considered a minor species.

2. Scientific Overview

This MUMS application for meloxicam 0.5 mg/ml oral suspension for guinea pigs includes documentation from one laboratory study (P 05 BIVI 001) where the pain reducing potential of meloxicam was evaluated in guinea pigs subjected to soft tissue surgery (castration), and one target animal safety (TAS) study (Study no 33608).

2.1. Dose determination

No dose determination/confirmation studies have been performed by the applicant.

The proposed oral dose of meloxicam (0.2 mg /kg body weight induction dose followed by a once daily dose of 0.1 mg/kg body weight for two additional days) was supported by expert opinions and published data from uncontrolled studies and case reports using doses ranging between 0.1 and 0.5 mg/kg administered once or twice daily. Safety and efficacy with respect to pain relief of meloxicam was not objectively evaluated in the studies provided.

Administration of Metacam with small amounts of food, e.g. treats, could be difficult; also palatability of the product for guinea pigs has not been demonstrated. To ensure accurate dosing, administration should be restricted to the use of a suitable syringe. To avoid dosing errors caused by a mixing up of the dosing instructions with those for the treatment of cats, the product information advises the user to place a small amount of the product in a small container (teaspoon) first, and then draw the correct amount from this container into a syringe. In addition, it is suggested to include a warning against using the cat syringe.

Given that this application is classified as MUMS, the approach to dose selection was considered adequate. The efficacy of meloxicam when administered at the selected dose was evaluated in a single laboratory study (see below).

2.2. Efficacy of postoperative pain relief in guinea pigs (Study P 05 BIVI 001)

The aim of the GCP-compliant laboratory study was to determine if Metacam 0.5 mg/ml oral suspension was effective in reducing post-operative pain after soft tissue surgery in guinea pigs.

The pivotal clinical study was a blinded, randomised and placebo controlled trial, involving 30 male guinea pigs undergoing surgical castration.

The animals were kept in groups of three in cages and allocated to two treatment groups: meloxicam treatment (n=15) and placebo treatment (n=15). An induction dose of 0.2 mg meloxicam/kg body weight was administered orally to the meloxicam group approximately 45 min prior to surgery, and a maintenance dose of 0.1 mg meloxicam/kg body weight administered orally was used on each of the following two days. In order to observe the animals, each group was video recorded three times daily for one hour at a time, according to a pre-set schedule over 4 days (days -1, 1, 2 and 3), and used to determine the frequency of feed and water intake, as well as the behaviour of the animals (activity, alertness and aggression against cage mates).

The primary endpoint was the cumulative frequency of feeding during the day of surgery and the two following days. Feeding behaviour is considered to be correlated with expression of pain in the guinea pig, and increased feeding frequency is accepted as a surrogate marker for pain relieving effect of treatment. Several other parameters such as heart rate, respiratory rate, body weight, food and water consumption, behaviour, clinical appearance were used as secondary endpoints.

With regard to the primary endpoint, a significantly higher (p=0.049) cumulative feeding frequency was noted in the meloxicam treated group (240±35 feeding events) as compared to the placebo group (207±40 feeding events). None of the secondary endpoints provided support for a pain reducing effect of meloxicam.

Regarding the clinical relevance of the treatment effect observed, the applicant argued that, in general terms, it is of value to reduce the depression in feed intake for smaller mammals since this will reduce the risk for metabolic disorders and disturbances in the gut flora.

No adverse events or clinical abnormalities were observed during the clinical examinations.

Conclusions:

A statistically significant difference in cumulative feeding frequency over three days was demonstrated between the treatment and the placebo groups in favour of the treatment group. The majority of CVMP members accepted the applicant's explanation that feeding behaviour is considered to be correlated with expression of pain in the guinea pig, and accepted the feeding frequency as a surrogate marker for pain relieving effect of treatment.

2.3. Target animal safety

In support of the tolerance of Metacam in guinea pigs, the applicant provided a GLP-compliant target animal safety study evaluating the safety of Metacam 0.5 mg/ml oral suspension in guinea pigs, when given as an oral dose repeated over 9 consecutive days. In addition, a GLP-compliant dermal safety study in guinea pigs (study no. I01-89) was provided as supplementary information.

The pivotal target animal safety study (Study no 33608) included 32 animals (16 males and 16 females, 40-day-old) divided into four study groups. One group was treated with placebo and three groups were treated with 0.2, 0.4 or 0.6 mg meloxicam/kg body weight daily on the first three days, corresponding to 1x, 2x and 3x of the proposed recommended induction dose. On the following 6 days, half of the initial daily doses were given to maintain the same multiples (1x, 2x and 3x) of the proposed maintenance dose.

The animals were observed individually before and after dosing for any signs of behavioural changes, reaction to treatment or illness. Blood samples were taken before study start and at completion of the treatment period and analyses for haematology, coagulation and blood biochemistry were performed. Urine was also taken before and after the study period and analysed. Food and water intake per animal was calculated. Necropsy was performed on day 10 and histopathology subsequently carried out on 16 of the animals (the placebo group and the 3x dose group).

No clinical changes were observed and none of the animals showed any behavioural changes during the study. Body weight did not change significantly during the study in any of the groups and the faeces had normal consistency in all animals. There was no difference in food consumption between the test groups. There were several significant changes in haematology and blood biochemistry but a dose response relationship was not evident and a relationship to treatment was not confirmed. An apparent difference in urine creatinine was noted but this was due to changes within the placebo group for which there were no obvious explanation. Blood parameters that could reflect an effect of NSAID treatment, such as creatinine, remained within normal range. Slight changes observed in the mucosa of the oesophagus may have been related to the fact that animals were treated via gavage.

The results from the clinical study, where meloxicam was generally well tolerated at the recommended dose (see above) confirmed the results of this study.

In addition to the pivotal study, the applicant also provided a supportive dermal safety study (no I01-89) including 34 guinea pigs (20 test, 10 placebo, 4 DNCB (dinitrochlorobenzene) positive control). Meloxicam 2.5 mg/kg body weight was administered intradermally and epicutaneously to the test group two times with an interval of 15 days between treatments. No dermal sensitisation reactions appeared to be triggered by the treatment with meloxicam 2.5 mg/kg body weight.

Conclusions:

It can be concluded that meloxicam is well tolerated in guinea pigs at the recommended dose, and no treatment related adverse events were noted at doses up to 3x the proposed dose for 3 times longer than recommended.

The PSUR cycle for Metacam does not have to be restarted, provided all adverse events (i.e. including non-expedited) continue to be reported directly into the EVVet database. Where any change to the electronic reporting procedure is intended by the marketing authorisation holder (i.e. if non-expedited reports cease to be reported electronically) this should be communicated to the Agency as soon as possible for re-consideration of the PSUR reporting requirements.

4. Benefit-risk assessment

4.1. Benefit assessment

The potential benefit would be to alleviate mild to moderate post-surgical pain after soft tissue surgery such as male castration in guinea pigs. A pain-relieving effect of treatment was demonstrated as an increase in cumulative feeding frequency during three days after male castration compared to placebo. Feeding behaviour is considered to be correlated with expression of pain in the guinea pig, and the feeding frequency is accepted as a surrogate marker for a pain alleviating effect of treatment.

4.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Safety data was presented from one target animal safety study and one clinical study including laboratory animals. According to the outcome of these studies the treatment is well-tolerated and the selected dose is well tolerated at up to three times the recommended dose. Adverse signs related to the toxicity targets for meloxicam (kidneys, gastro-intestinal tract) were absent.

No user risk assessment was provided. The addition of the new target species guinea pig to the currently authorised product Metacam 0.5 mg/ml oral suspension for cats was considered not to alter the risk for the user.

The proposed new indication would not affect environmental safety.

4.3. Evaluation of the benefit-risk balance

Pain alleviation of treatment at the recommended dose was demonstrated in a placebo-controlled study via the surrogate parameter feeding frequency. Target animal tolerance shows that treatment is

well tolerated at the recommended dose, and there is no foreseen altered risk to the user or the environment.

The CVMP acknowledged that the data supporting the efficacy in the proposed indication for guinea pigs are rather limited; however, there are no recognised models to investigate this indication in the target species, and guinea pigs are considered a "minor species". In the absence of any alternative authorised treatment options for this indication, and in view of the wide safety margin of meloxicam at the recommended dose, the Committee considered that for animal welfare reasons, the limited data package would be acceptable.

The benefit risk balance is therefore considered to be positive.

The PSUR cycle for Metacam does not have to be restarted, provided all adverse events (i.e. including non-expedited) continue to be reported directly into the EVVet database.

The applicant has partially updated the product information in line with current QRD template v8.1, and has provided a commitment to update the outstanding wording in section 4.6 in the SPC (and section 6 in the package leaflet) relating to the frequencies of adverse reactions in line with the convention for frequency groupings. A proposal and rationale for the proposed modifications should be submitted by the applicant together with the next PSUR, and changes should then be implemented with the next variation affecting the product information.

4.4. Conclusions

Based on the original and complementary data presented on efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded by majority 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 (Commission Regulation (EC) No. 1234/2008), for addition of the non-food producing target species, guinea pigs, with the accompanying indication: "Alleviation of mild to moderate post-operative pain associated with soft tissue surgery such as male castration".

The CVMP considers by majority 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 Annexes to the Community marketing authorisation.

I, IIIA, IIIB