EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines and Product Data Management

EPAR worksharing type II variation for Metacam (EU/2/97/004/001, 007-008, 010, 014-015, 027-028, 031-032, 035-038) and Novem (EU/2/04/042/001-014)

International non-proprietary name: Meloxicam

Procedure No.

EMEA/V/C/000033/WS/0264

EMEA/V/C/000086/WS/0264

Scope:

Worksharing type II variation No. C.I.6.a – to add a new therapeutic indication ("dehorning claim") to the product literature due to new clinical data.

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 20 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) on 30 March 2012 an application for a worksharing type II variation for Metacam and Novem.

1.1.1. Scope of the variation

Worksharing type II variation (C.I.6.a) to add a new therapeutic indication ("dehorning claim") to the product literature due to new clinical data.

Current	Proposed
SPC: **Metacam 5 mg/ml solution for injection for cattle and pigs and Novem 5 mg/ml solution for injection for cattle and pigs** **4.2 Indications for use, specifying the target species** **Cattle:** For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle. For use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle. **4.4 Special warnings for each target species** Treatment of piglets with Metacam before castration reduces post operative pain. To obtain pain relief during surgery co-medication with an appropriate anaesthetic/sedative is needed. To obtain the best possible pain relieving effect post surgery Metacam should be administered 30 minutes before surgical intervention. *Corresponding sections of labelling and package leaflet have been amended accordingly.*	SPC: **Metacam 5 mg/ml solution for injection for cattle and pigs and Novem 5 mg/ml solution for injection for cattle and pigs** **4.2 Indications for use, specifying the target species** **Cattle:** For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle. For use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle. For the relief of pain following dehorning. **4.4 Special warnings for each target species** Treatment of cattle with Metacam before dehorning reduces post operative pain. To obtain pain relief during surgery co-medication with an appropriate anaesthetic/sedative is needed. To obtain the best possible pain relieving effect post surgery Metacam should be administered 10 minutes before surgical intervention. Treatment of piglets with Metacam before castration reduces post operative pain. To obtain pain relief during surgery co-medication with an appropriate anaesthetic/sedative is needed. To obtain the best possible pain relieving effect post surgery Metacam should be administered 30 minutes before surgical intervention. *Corresponding sections of labelling and package leaflet have been amended accordingly.*
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2. Scientific discussion

2.1. Assessment

Introduction

The current procedure concerns the adding of the following claim for cattle in section 4.1 of the SPC: *for the relief of pain following dehorning*. Furthermore, appropriate warning statements in section 4.4 of the SPC relating to the new indication are proposed.

Information to support the new indication is:

- Pilot study (exploratory and not dimensioned to gain conclusive information);
- Published data describing the potential pain relieving effect of Metacam following dehorning (pivotal study). In addition to this, published data are presented to clarify pain expression and pain assessment in general and during dehorning and the role of NSAIDs to alleviate pain. Disbudding refers to the removal of the horn buds in young calves before any horn can be seen. Dehorning refers to amputation of grown out horns in mature animals. Surgical means or heat cauterisation is used and local or general anaesthesia is applied in animals over four weeks of age. Published data demonstrates that dehorning is connected to significant pain perception, as measured by behavioural and physiological changes, which persists for at least 24 hours. No gold standard exists with regard to pain assessment. Different behavioural parameters, possibly in combination with cortisol measurement, is regarded to accurately reflect pain perception. The effect of local anaesthetics during dehorning has been explored in several studies. Local anaesthesia administered around each corneal nerve appears to effectively reduce pain in the immediate period after dehorning but a cortisol rise 2 hours after surgery indicates pain development as the effect of the anaesthesia wanes. Several studies have been made where different NSAIDs are combined with local anaesthesia to prolong pain relief.
- All data is presented and discussed in a Critical Summary. It is mentioned that to ensure appropriate treatment of the acute pain caused by and during the dehorning procedure, co-medication with a local anaesthetic is needed and consequently a recommendation for such

medication is proposed to be added to the SPC. According to literature, pain caused by dehorning occurs in two phases where the first phase needs to be controlled by appropriate anaesthesia whereas for the second phase which is claimed to be related to inflammatory pain could be alleviated by NSAID treatment.

Pharmacokinetics

No new data on pharmacokinetics are submitted in relation to this application. In a pivotal clinical field study of Heinrich et al. (2009; 2010) Metacam 20 mg/mg solution for injection was administered by the intramuscular (i.m.) route. The submission by the applicant however, is for the subcutaneous (s.c.) and intravenous (i.v.) routes of administration of Metacam 5 mg/ml and Metacam 20 mg/mg solution for injection.

To support comparable exposure during i.m. administration as compared to i.v. and s.c. the applicant referred to a previously submitted study determining bioavailability of 92 % of Metacam 5 mg/ml in calves on the basis of s.c. and i.v. administration of 0.5 mg/kg body weight and arguing no evidence for significant difference in bioavailability between s.c. and i.m. administration. Although no data on bioavailability after i.m. administration in cattle are available, corresponding data from swine demonstrate bioavailability after i.m. administration of 87 % for Metacam 5 mg/ml and 100 % for Metacam 20 mg/ml solution for injection. Finally it is mentioned that in general i.m. injection is considered to be intermediate between s.c. and i.v. administration regarding C_{max} and T_{max}. Furthermore, given the high bioavailability AUC can reasonably expected to be uninfluenced by any difference between i.v. and i.m. injection.

The applicant's arguments were accepted. It is reasonable to assume that any difference in exposure between i.m. and s.c. administration would be of a limited magnitude and the level of enzyme inhibition would thus be comparable. Consequently it would be possible to extrapolate efficacy data from the pivotal study in which i.m. administration was applied, to the authorised administration routes (s.c. and i.v.).

Tolerance

Reference is made to previously submitted tolerance data, which is acceptable.

Dose finding

The applicant referred to previously submitted data to justify the dose which is the same as already authorised for other indications in cattle (0.5 mg/kg body weight). The appropriateness of the proposed dose (0.5 mg/kg body weight) was regarded as sufficiently supported through the positive outcome of the clinical studies and on account of the previous authorisations for other indications for cattle where this same dose was used.

Clinical studies

To support clinical efficacy for the new indication the applicant presented one new pilot study and data from published studies presented in scientific journals. In the Critical Summary the published studies by Heinrich et al. (2009; 2010) are regarded to provide pivotal information whereas the pilot study is regarded as exploratory and not dimensioned to provide conclusive information. The studies are summarised below.

A pilot study evaluating the efficacy of bovine Metacam in controlling pain following dehorning

A non GCP one site randomised placebo controlled complete block design study performed in the USA in 2004.

Forty two calves were used distributed in 7 cohorts, with 6 calves per cohort. Cohorts 1–5 contained 30 animals aged 8–12 weeks. Ten animals were injected treatment i.v. (group 1), 10 s.c. (group 2) and 10 placebo treatment (group 3). Cohort 6 contained 6 calves aged 16–24 weeks; 2 injected treatment i.v. (group 1), 2 s.c. (group 2) and 2 placebo treatment (group 3). Cohort 7 contained 6 animals aged 8–15 weeks. They were not co-medicated with local anaesthetics. Three animals were i.v. treated (group 1) and 3 were injected with saline control i.v.

Test treatment was Metacam 20 mg/ml solution for injection, 0.5 mg/kg body weight, once. Meloxicam was administered subcutaneously or intravenously 5–20 minutes prior to beginning of dehorning. Placebo treatment was the test article devoid of active substance (cohorts 1-6).

Saline control was 0.9 % sodium chloride (cohort 7). Local anaesthetic (lidocaine 2 %) was administered to cohort 1–6, 5 ml subcutaneously around each corneal nerve before dehorning. The calves in cohorts 1–5 and cohort 7 were dehorned by use of Rhinehart X50 electrocautery dehorner whereas in cohort 6 Barnes dehorner (cutting device) was used. The calves in cohorts 1–6 were given local anaesthetics.

Efficacy endpoint

Pain assessment. Behavioural activities and a VAS scoring system (0–100) was applied for efficacy assessment. Assessments were performed repeatedly (2, 4, 6, 8, 10, 12 and 24 hours after dehorning in cohort 1–5 and 2, 4, 6 and 8 hours after dehorning for cohort 6 and 7) during the first 24 hours after dehorning and during 18 minutes at each observation occasion. The behavioural frequency of the following parameters was monitored: tail shaking, head rubbing, ear flicking, head shaking and scratching.

Statistical analyses. Cohorts 1–5 were combined for statistical analysis, whereas cohort 6 and cohort 7 were analysed separately. Data for variables (behavioural activity scores, visual analogue score) measured multiple times over the course of the study were statistically evaluated using a repeated measures analysis of covariance (RMANCOVA) using SAS PROC MIXED.

Results

Behavioural parameters (tail shaking, head rubbing, ear flicking, head shaking and scratching) and VAS for cohort 1–5

No significant overall difference among treatments was noted. No significant treatment x time interactions were noted.

Behavioural parameters for cohort 6 and 7

No significant treatment-related differences were seen between the treatment groups for the different efficacy endpoints.

CVMP concluded that this small study was regarded to be of an exploratory nature and, furthermore to provide no significant support for a pain alleviating effect of meloxicam in young calves given local anaesthesia and being dehorned with electrocautery equipment.

In addition to this study the applicant refers to published studies to further support the new indication. This information is summarised below.

The impact of meloxicam on postsurgical stress associated with dehorning (Heinrich A et al., J. Dairy Sci., 2009)

Objective: To determine the duration of the stress response associated with cautery dehorning and to assess the effectiveness of the non-steroidal anti-inflammatory drug meloxicam for reducing that response.

Date: 2005–2006.

Animals: 60 Holstein heifers, age 6-12 weeks.

Design: Randomised and placebo controlled study.

Test substance: Meloxicam (Metacam) 20 mg/ml solution for injection.

Placebo: Metacam vehicle.

Study procedure: All calves were given lidocaine (2 % with 0.05 mg/ml of epinephrine) corneal nerve block, 5 ml per side, 10 minutes before dehorning. To establish baseline values, calves were sham dehorned 24 hours before actual dehorning. Dehorning was made with Rhinehart X30 electrocautery dehorner.

Test animals (n=30) were given a single dose of Metacam 0.5 mg/kg body weight.

Blood sampling: taken 0, 0.5, 1, 1.5, 2, 4, 6 and 24 hours after dehorning.

Heart and respiratory rate: Monitored at same time points as blood samples were taken.

Efficacy endpoints: Plasma cortisol, heart and respiratory rate.

Statistical analysis: Procedure MIXED. Measurements taken after the sham procedure were included as covariates to determine the difference between sham and actual dehorning.

Results:

Overall calves had higher respiratory rates after dehorning compared with sham treatment; however the increase was greater for control calves (average increase of 2±0.1 rpm and 4±0.2 rpm for meloxicam and control, respectively, $p<0.001$).

Elevation in cortisol was significantly less for meloxicam treated calves from the time of dehorning (0 h) until 6 h after the procedure but there was no difference between the treatment groups at 24 h (meloxicam 35.2 ± 2.74 nmol/l, control 34.8 ± 3.64 nmol/l; P = 0.13).

Overall, elevation in heart rates was less for meloxicam-treated calves after dehorning (increase meloxicam 3.74 ± 0.96 bpm, control 4.70 ± 1.87 bpm; P = 0.04).

This study was considered to bring support for a pain relieving effect of Metacam after dehorning although it was noted that potential effects between 6 and 24 hour-post surgery was not explored and no effect was evident 24 hours after dehorning. In this study the calves were administered Metacam i.m. which is not in accordance to recommendations (subcutaneously or intravenously). However, it was considered reasonable to assume that any potential difference in exposure between s.c. and i.m. administration of the same dose would be marginal and enzyme inhibition pattern similar for the two routes of administration. Thus, efficacy data generated after i.m. exposure as in this study was regarded useful to conclude on efficacy during s.c. and i.v. administration.

The effect of meloxicam on behavior and pain sensitivity of dairy calves following cautery dehorning with a local anesthetic (Heinrich A et al., J. Dairy Sci. 2010)

In this publication, data concerning monitoring of different behavioural parameters are presented from the study presented above ("The impact of meloxicam on postsurgical stress associated with dehorning"; Heinrich A et al., J. Dairy Sci., 2009).

Efficacy parameters:

- Continuous sampling of behaviour was performed during five 1 h intervals using video recordings.

- Total daily activity was monitored using an accelerometer until 24 hours after dehorning.
- A pain sensitivity test was performed 4 hours after dehorning, with a pressure algometer provided with a rubber tip that was pressed against 4 different areas close to the horn bud with increasing force until the calf withdrew its head.
- Feed and water intake were recorded daily.

Statistical analyses: Behavioural data were analysed using a negative binomial distribution (procedure glimmix in SAS). Observations from the sham procedure were used as covariate to determine the change from baseline. Random effects of trial and of repeated measures on calf were included in the model.

Results

Ear flicks: There was an effect of treatment on ear flicking behaviour. There were increases of 4.29 ± 1.10 and 1.31 ± 0.66 ear flicks/h on Day 0, and increases of 3.27 ± 0.89 and 0.55 ± 0.50 ear flicks/h on Day 1, for control and meloxicam calves, respectively ($F = 10.65$, $df = 16$, $P = 0.005$).

Head shaking: Increased head shaking in control calves was greater ($P < 0.05$) than in meloxicam calves for 9 h following dehorning, after which there were no significant treatment effects. Control calves displayed 2.53 ± 0.54 more head shakes/h after dehorning, whereas meloxicam calves displayed an increase of 0.85 ± 0.46 head shakes/h.

There were no significant effects of treatment on head rubbing or tail flicking.

The accelerometer activity devices indicated that meloxicam calves were less active for the first 5 h following dehorning (activity 34.1 ± 3.2 and 30.6 ± 2.6 for control and meloxicam respectively; $P = 0.02$).

Pain sensitivity

Meloxicam calves displayed less sensitivity to pain in the pressure algometry test following dehorning compared with control calves (MNT = 1.62 ± 0.13 kgf and 2.13 ± 0.15 kgf for control and meloxicam, respectively; $F = 8.84$, $df = 55$, $P = 0.004$). Although all calves showed decreased tolerance to pressure following dehorning ($P = 0.04$), control calves were nearly twice as sensitive as meloxicam calves (decrease in MNT of 0.94 and 0.55 for control and meloxicam, respectively).

Feed consumption

Overall, feed intake did not differ between the treatments; however, there was a trend for meloxicam calves to consume more feed on Day 1 than on Day 0 ($P = 0.07$).

This study was considered to bring further support for a pain reducing effect of Metacam when given as a single dose of 0.5 mg/kg body weight to calves concomitantly treated with local anaesthesia. Differences in behavioural parameters between Metacam and placebo treated animals suggested an effect of treatment up until 20 hours after dehorning. In this study the animals were provided Metacam i.m. However, as previously mentioned it is assumed that corresponding effects is obtained after s.c. or i.v. administration as is the recommended route of administration.

Effects of local anaesthetic and nonsteroidal anti-inflammatory drug on pain responses of dairy calves to hot-iron dehorning (Stewart M et al., J. Dairy Sci. 2009)

Objective: To assess pain response from time of dehorning until 3 hours later, when the effect of local anaesthesia wanes and to explore the influence of NSAID treatment during this period.

GCP status: No.

Animals: Forty-six (46) Holstein-Friesian calves, age 33±0.3 days (range 30-39 days).

Design: Randomised, placebo controlled experimental study.

Test substance: Metacam.

Study procedure:

Six treatment groups were formed:

1. **Control.** Saline injected around the corneal nerve and handled to simulate dehorning, (n=8).
2. **DH.** Hot-iron dehorned saline injected around the corneal nerve and dehorning with a gas-powered cautery iron (n=6).
3. **LA+DH**. Hot-iron dehorned local anaesthesia injected around the corneal nerve and and s.c. around the base of each horn bud (2 % lignocaine hydrochloride), 10 minutes before dehorning (n=6).
4. **LA control**. Sham dehorning, local anaesthesia injected as previously described (n=8).
5. **LA and NSAID control**. Sham dehorning, local anaesthesia injected as previously described, Metacam (0.5 mg/kg body weight) injected i.v. 30 minutes before sham dehorning (n=8).
6. **LA+NSAID+DH**. Hot-iron dehorned, local anaesthesia injected as described previously, Metacam (0.5 mg/kg body weight) injected i.v. 30 minutes before dehorning (n=8).

Efficacy endpoints:

Eye temperature measured by means of infrared thermography. Measured every 5 min for 3 hours after treatment.

Heart rate monitored via a device strapped onto the chest of each animal.

Statistical analysis: Analysis of variance was applied and the change between before and after 2.5 hours after dehorning was analysed to assess pain response during the time when the effect of the local anaesthesia disappears.

Results:

There were differences between treatments (P = 0.011) in the change in eye temperature between 2 and 3 h (P = 0.011); eye temperature decreased by 0.6 $\pm$ 0.1 °C during this time (P < 0.001) following DH with LA. There were no significant differences in eye temperature between 2 and 3 h after DH for any other treatments (P ≥ 0.129).

There were no treatment differences in HR at 2.0 to 2.5 h (93 $\pm$ 4.9 bpm, P = 0.190) or at 2.5 to 3.0 h (94 $\pm$ 5.3 bpm, P = 0.140). There were differences in the change between these 2 time periods (*P* = 0.049): HR increased by 8 $\pm$ 3.0 bpm (*P* = 0.013) for the LA+DH group (2.0 to 2.5 h: 98 $\pm$ 4.8 bpm vs. 2.5 to 3.0 h: 106 $\pm$ 5.2 bpm). No other treatments showed significant changes in HR between 2 to 3 h (P ≥ 0.073).

The fact that in this study changes between groups were subtle and the correspondence between the changes noted and a proposed pain alleviating effect of Metacam is not fully evident this study was not regarded to provide support for the proposed new indication.

Environmental impact assessment of the new indication

The applicant has submitted an EIA in line with VICH GL 6 "Guideline on Environmental Impact Assessment (EIA) for Veterinary Medicinal Products- Phase I" (CVMP/VICH/592//98-FINAL) and

"Revised Guideline on Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH GL 6 and GL 38" (EMEA/CVMP/ERA/418282/2005-Rev.1).

When used to alleviate pain associated with dehorning, Metacam solutions for injection will be administered s.c. or i.v. Both administration routes at the same dosage of 0.5 mg/kg are already registered in the EU. However, the dehorning-indication needs a new environmental impact assessment as the proportion of animals in a herd that are treated may be different from other registered indications.

The Phase I assessment ends in question 17 because the predicted environmental concentration of the veterinary medicinal product in soil (PEC soil) is to be 2.9 µg/kg (less than 100 µg/kg). This is based on the assumption that cattle are treated once with 0.5 mg/kg body weight. The fraction of the herd to be treated was assumed to be 100 %. This is not considered to be realistic but presents the worst case scenario. As also under this assumption PEC soil is below 100 µg/kg, all scenarios with a smaller proportion of the herd being treated are covered.

PEC soil [µg.kg-1] = (0.5 x 1 x 140 x 1.8 x 170 x 1 / 1,500 x 10,000 x 0.05 x 10 x 1) x 1,000

The environmental safety statements in the summary of product characteristics are adequate.

It was concluded that the applicant provided a conservative EIA considering the new indication in accordance with the current guidelines. It was further agreed that the environmental statements in the SPC are adequate.

2.2. Summary and Conclusions

The current application concerns adding a claim for pain relief after dehorning of cattle and involves the 5 mg/ml and 20 mg/ml solution for injection. No change in the previously authorised dosing strategy for these formulations is proposed (0.5 mg/kg body weight as a single dose). No data were submitted to support the relevance of the approved dose for the new indication which constitutes the first direct claim for a pain relieving effect in cattle for the current formulations. This was regarded acceptable in account of the positive outcome of the clinical studies submitted in support of the current indication and in account of the previous authorisations of other indications for cattle where this same dose was used.

One single administration is recommended for the hitherto approved indications. According to the efficacy data submitted, pain associated to dehorning of young calves can persist for up to 48 hours. It appears from this information as some pain relieving effect of Metacam persists beyond 24 hours and it would therefore be sufficient to recommend only one single administration.

No new tolerance data were submitted which is acceptable in account of no change in posology is proposed as compared to previous authorisations for the two formulations. Safety data from the efficacy studies provided in connection to this application supports acceptable tolerance.

To support efficacy according to the proposed new indication which regards relief of pain following dehorning the applicant provided one pilot study in which in total 42 calves were given one dose of Metacam (20 mg/ml solution for injection, 0.5mg/kg body weight) and were dehorned 5–20 minutes later by use of an electrocautery dehorner. Three cohorts were created to explore the pain alleviating potential in young calves 8–12 weeks of age, older calves 16–24 weeks of age, and young calves which were not provided local anaesthesia in connection to dehorning. The study was of exploratory nature and thus not powered on basis of pre-set assumptions regarding effect level which restricted the possibility to gain statistically supported outcomes. Regarding the cohort including older calves and younger calves not provided local anaesthesia no significant differences as compared to placebo was noted. For the larger cohort containing young calves co-medicated with a local anaesthetic no clear

picture of a pain alleviating effect was noted during 24 hours after dehorning, as measured by different behavioural endpoints and a visual analogue scale. Nevertheless, a statistically supported advantage of Meloxicam treatment as compared to placebo was noted for some endpoints at certain time points. No adverse events were noted in this study. The study was not regarded to bring any significant support for the new claim.

Pivotal support for the current application was sought in two published studies by Heinrich et al. (2009, 2010) which presented data from one experimental study. In this well conducted study 60 heifers aged 6–12 weeks, divided in placebo and test groups were given local anaesthetics and a single recommended dose (0.5 mg/kg body weight) of Metacam before they were dehorned with an electrocautery dehorner. Sham dehorning preceded the actual dehorning and the pain alleviating effect, based on assessment of plasma cortisol, heart and respiratory rate and several behavioural parameters was determined during 44 hours on basis of change from baseline levels. During the whole or parts of the follow up period statistically significant differences were noted for cortisol change, respiratory rate, heart rate, ear flicks, head shaking, general activity and pain sensitivity around the horn, pointing towards a pain alleviating effect of Metacam after dehorning in young calves co-medicated with a local anaesthetic. The study outcome is regarded to bring substantial support for a pain alleviating effect of Metacam after dehorning. Some minor additional support is gained from yet another experimental study.

A concern was raised regarding the fact that in the above mentioned pivotal study Metacam was administered intramuscularly whereas the current application concerns the administration of Metacam 5 mg/ml and 20 mg/ml according to the previously authorised routes for cattle which is subcutaneously or intravenously. PK data regarding intramuscular administration in cattle is not available. The applicant mentioned that previously submitted bioavailability data for cattle demonstrated 92 % bioavailability after subcutaneous administration. Bioavailability data regarding intramuscular administration in swine demonstrated similar high levels; 87 % for Metacam 5 mg/ml solution for injection and 100 % for Metacam 20 mg/ml solution for injection. It was further argued that bioavailability for intramuscular administration is most often in between subcutaneous and intravenous administration and given the high bioavailability demonstrated for subcutaneous administration in cattle AUC would reasonably be expected to be uninfluenced by any difference between i.v. and i.m. administration. The applicant's arguments were accepted. It was considered reasonable to assume that any potential difference in exposure between s.c. and i.m. administration of the same dose would be marginal and enzyme inhibition pattern similar for the two routes of administration. Thus, efficacy data generated after i.m. exposure as in this study was regarded useful to conclude on efficacy during s.c. and i.v. administration. In the pivotal efficacy study the 20 mg/ml solution for injection was used. The applicant referred to previously confirmed bioequivalence between this formulation and the 5 mg/ml solution for injection to support that the indication is given to both formulations, which was regarded acceptable supported.

To conclude, the information submitted was regarded to bring sufficient support for a pain alleviating effect of Metacam after dehorning of young calves. The new indication would have to be restricted to calves so as to reflect the study population.

The CVMP agreed on the new indication:

> "For the relief of post-operative pain following dehorning in calves".

The appropriate additional warning in product information should be as follows:

> "Treatment of calves with Metacam 20 minutes before dehorning reduces post-operative pain. Metacam alone will not provide adequate pain relief during the dehorning procedure. To obtain adequate pain relief during surgery co-medication with an appropriate analgesic is needed."

Corresponding conclusions can be drawn for Novem involved in this work sharing procedure.

3. Benefit-risk assessment

3.1. Benefit assessment

Administering Metacam and Novem to young calves before dehorning would reduce pain perception during the post-operative period.

3.2. Risk assessment

The risks related to treatment with Metacam or Novem are well known and appropriate information and risk mitigation measures are described in the SPC.

3.3. Evaluation of the benefit-risk balance

Sufficient data have been presented to support a pain alleviating effect of Metacam and Novem after dehorning of young calves. Provided the risk mitigation measures mentioned in the product information are applied the risks connected to Metacam and Novem treatment are outweighed by the benefits demonstrated for the proposed new indication. The benefit-risk balance remains unchanged.

No change to the impact on the environment is envisaged.

4. Overall conclusions of the evaluation and recommendations

The CVMP considers 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.

4.1. Changes to the community marketing authorisation

Changes are required in the following annexes of the Community marketing authorisation:

- Annexes I, IIIA and IIIB.