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Veterinary Medicines and Product Data Management

CVMP assessment report
RevitaCAM (EMEA/V/C/002379)

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

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Introduction

An application for the granting of a community marketing authorisation of RevitaCAM 5 mg/ml oromucosal spray for dogs has been submitted to the Agency on 10 December 2010 by Abbott Laboratories Ltd in accordance with Regulation (EC) No. 726/2004.

The Committee confirmed in October 2010 elibigility for the centralised procedure as a hybrid abridged application (as described in Article 13(3) of Directive 2001/82/EC as amended) under Article 3(3) of Regulation (EC) No. 726/2004 with Metacam Oral Suspension for Dogs as the reference product.

RevitaCAM 5 mg/ml oromucosal spray for dogs contains meloxicam as the active substance and is presented in packs/containers of 10, 20 and 50 ml. It is indicated for the alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders. The route of administration is oral as it is an oromucosal spray. The target species is dogs.

Part 1 - Administrative particulars

Detailed Description of the pharmacovigilance system (DDPS)

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. It is considered that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Union or in a third country.

GMP status

The necessary declaration of the compliance of the manufacture of the active substance with EU GMP requirements for starting materials has been provided from the qualified person of the site of batch release.

The GMP certification provided by the UK inspection authority for the site of finished product manufacture is with respect to human medicines only. However, an inspection of the site was triggered by this centralised application and a site inspection was carried out by the UK inspection authorities in July 2011, which confirmed that the manufacture of non-sterile liquids for internal use is covered by the GMP certificate issued. An updated GMP Certificate has been provided, covering veterinary medicinal products.

A Dutch manufacturing authorisation was provided, covering import and batch release of veterinary medicinal products. The approved site of batch release is Abbott Logistics Minervum 7201, Breda 4817 ZJ, The Netherlands.

Part 2 - Quality

Composition

The proposed veterinary medicinal product contains 5 mg/ml of meloxicam in an aqueous solution with ethanol as a preservative. The product also contains polycarbophil as a viscosity modifier, which is dispersible in the solvent system and is considered to be a colloidal dispersion that can readily be homogenised on shaking. Also present in the formulation are boric acid and potassium chloride as buffers, along with sodium hydroxide and hydrochloric acid for pH adjustment.

Container

The product is presented in 10 ml, 20 ml or 50 ml Type I clear glass vials and polypropylene screw caps with laminated film liners. A metered dose pump is provided with each of the vial sizes which deliver a dose of 50 µl, 100 µl or 215 µl respectively.

Development pharmaceutics

The aim of the development pharmaceutics was to develop a product that is bioequivalent to the reference product, Metacam 1.5 mg/ml oral suspension, and although the product concentration and route of administration are different to that of the reference product, the product was developed to ensure that the dose administered by the metered dose spray is equal to that administered with the reference product. The initial formulation developed led to concerns about the complicated compounding process and possible reactions causing precipitates and a fall in pH. Process development was carried out in order to replace the original complicated compounding process with a simpler "sequential addition" manufacturing method. The product contains a viscosity enhancer to aid delivery and improve the bio-adhesive properties of the formulation. Content uniformity data was provided on laboratory batches manufactured with viscosities above and below the proposed limits and all results were within the requirements of 85 – 115%. In addition, droplet size distribution results were provided for these batches which demonstrated that a higher percentage of respirable droplets are seem with the lower viscosity batches however even at the lowest viscosities less than 2% of the dose volume is seen to be respirable, and this considered to have no adverse impact on the safety or efficacy of the product. Spray content uniformity studies were performed, however they were not in accordance with the requirements of the Uniformity of Delivered Dose testing for metered-dose oromucosal sprays as detailed in the European Pharmacopeia (Ph. Eur.) dosage form monograph for oromucosal preparations and justification was requested. The applicant confirmed that the additional priming that was performed during the studies was in accordance with the results of the priming studies and that instruction on primimg, repriming and techniques to be employed in use have been added to the SPC and package leaflet. Priming, re-priming and clogging studies were also performed, along with studies to characterise the droplet size distribution and the spray pattern.

Method of manufacture

The manufacturing process consists of the manufacture of a polycarbophil slurry phase with boric acid and potassium chloride buffers in purified water. A meloxicam active phase is made with the addition of meloxicam to a solution of sodium hydroxide in purified water. Both of the phases are pH adjusted with sodium hydroxide or hydrochloric acid solutions. They are then combined, ethanol added and the pH adjusted if necessary. The volume is made up with purified water and then it is filtered, filled and sealed. The proposed batch size is 400 - 4000 kg and no overages are used. Process validation data has been provided for 3 pilot-scale batches of 400 kg, along with a bulk holding study on 1 of these pilot-scale batches.

Control of starting materials

Active substance

The data relating to the active substance is provided in an ASMF in the CTD format. The active substance is controlled according to the current Ph. Eur. monograph for meloxicam. Detail on the synthesis has been provided however, further information on the starting materials was requested and provided which justified the choice of starting material. There were also some issues raised with respect to the characterisation and impurities, and the analytical validation of a non-Ph. Eur. method,

however the requested additional information and documentation was provided and accepted. Tabulated batch analysis data was provided for production-scale batches from both of the proposed sites of manufacture. Further information was requested and provided regarding the reference standards.

Excipients

Boric acid, potassium chloride, anhydrous ethanol, sodium hydroxide, hydrochloric acid and purified water are controlled according to their Ph. Eur. monographs. Polycarbophil is controlled in compliance with the United States Pharmacopoeia (USP) monograph as no Ph. Eur. monograph exists for this excipient.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

None of the starting materials used for the active substance or for the excipients used in the finished product are risk materials as defined in Section 2 of the Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, EMEA/410/01 Rev. 2.

Control tests during production

Not applicable.

Control tests on the finished product

Specifications have been set for appearance, pH, viscosity, colour, identification and assay of the active and the preservative, related substances and microbial quality. In general, the proposed specification is acceptable and includes most parameters relevant to the dosage form including a test for Uniformity of Delivered Dose. Justification of the pH and viscosity limits was provided with respect to the stability and functionality of the product and was considered to be acceptable. The methods have been described in sufficient detail and the method validation provided demonstrates the suitability of the methods. Finished product batch analysis data was provided but was missing results for identification of the active and preservative and for specified micro-organisms. The applicant confirmed that identification by HPLC retention time was performed for these batches, and full compliance of these batches with microbiological testing was demonstrated at the initial time-point on stability. Confirmation was also provided that identification of the preservative was performed using the GC method. Batch Validity statements were provided for the reference standards.

Stability

For the active substance, a re-test period of 4 years, with no special storage conditions, is considered to be acceptable, based on the data submitted at accelerated conditions (40^{o}C/75% RH) and for long-term stability studies (at 25^{o}C/60% RH).

For the finished product, although the stability data provided indicates that the product is very stable, given that only 6 months data was provided for both the long-term and accelerated conditions, a maximum shelf-life of only 1 year was initially allowable. Further stability data was provided to 12 months at 25^{o}C/60% RH for 2 batches each of the 10 ml and 50 ml vials, with one of each inverted. No trending was noted for any of the parameters and all results were within the specifications and so a maximum shelf-life of 2 years is approvable. In addition, no differences were observed between the

results for the upright or the inverted vials at either storage condition. With respect to the in-use stability studies, all of the parameters tested showed very little variation to the proposed 6 month in-use shelf-life, with the exception of viscosity. A decreasing trend in viscosity is noted to Day 91 with an overall decrease apparent at 6 months. It was noted that all results were within the proposed in-use limits for viscosity however, results at Day 84 and Day 91 included out-of-specification results (i.e. with respect to the release and end-of-shelf-life specifications and suitable justification for the widening of the viscosity limits was requested. Again, data was provided for batches which demonstrated that a higher percentage of respirable droplets are seem with the lower viscosity batches however even at the lowest viscosities less than 2% of the dose volume is seen to be respirable, and this considered to have no adverse impact on the safety or efficacy of the product. It was also noted that no results were provided for microbiological quality in the in-use study. It was noted that the results for ethanol assay were consistent and without trend at 14-15% w/v (140 – 150 mg/ml), and given that preservative efficacy was demonstrated for product with 80% of the proposed ethanol content (120 mg/ml), the microbiological quality is not expected to be adversely impacted. Assurance has been provided that in-use stability testing will be performed on a batch of the finished product approaching end-of-shelf-life, including testing for microbial quality and preservative efficacy, in line with the requirements of the Note for Guidance EMEA/CVMP/424/01.

Other information

A declaration of compliance with VICH GL18 Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances and Excipients has been provided detailing the compliance of the product with the Option 1 criteria for class 2 solvents which are to be limited according to the guideline. Three options are available when setting limits for class 2 solvents and Option 1 covers products administered at less than 10g per day. Permitted daily exposure (PDE) is given in terms of mg/day and dose is given in g/day. These limits are considered acceptable for residual solvents in all substances, excipients, or products. Therefore this option may be applied if the daily dose is not known or fixed. If the residual solvents in all excipients and active substances in a formulation meet the limits given in Option 1, then these components may be used in any proportion.

In order to demonstrate that the proposed in-use lower limit of 2.0 cPs is consistent with acceptable spray characteristics, a sample with a viscosity of 2.0 cPs was tested for droplet size and spray pattern and the results were provided. Results obtained with samples with stated low and high viscosity had previously been provided. However, it was noted that no discussion of the comparative results was provided, nor was it stated what the actual viscosity results were for the previously provided low and high viscosity samples nor was any discussion of the impact or relevance of the results to the dosage form, in general, and the product, in particular. As indicated above, this was provided and the proposed viscosity limits are deemed to be acceptable.

Overall conclusions on quality

The dossier provides a suitable description and specifications for the active substance and the chosen formulation. Overall, it has been demonstrated that the production of the finished product leads to a product of consistent quality. In view of the standard production manufacturing process of the drug product and the provided validation data on pilot-scale, full scale validation may be performed post-approval. Data relating to the active substance is provided in an ASMF in CTD format. The excipients used in the manufacture of the finished product are of pharmacopoeial standard and so are acceptable. The container closure system chosen is suitable for the dosage form and the product. The finished product specification provides an assurance of the quality of the product and the tests comply with the requirements of the Ph. Eur. for the dosage form. In general, the analytical methods are well described and validation data confirm their suitability. Stability studies have been performed according

to relevant VICH guidelines. The stability studies conducted on the active substance allow a re-test period of 4 years, with no special storage conditions. For the finished product, the primary stability studies are on-going. A shelf-life of 2 years is acceptable for the finished product. The proposed in-use shelf-life of 6 months is considered acceptable.

Part 3 – Safety

Safety documentation

This application has been submitted in accordance with Article 13(3) of Directive 2001/82/EC, as amended (a hybrid generic application). The reference product is Metacam 1.5 mg/ml oral suspension.

Article 13(1) of Directive 2001/82/EC, as amended defines a generic medicinal product as a medicinal product "which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product and whose bioequivalence with the reference product has been demonstrated by appropriate bioavailability studies." However, RevitaCAM does not strictly meet the definition of a generic product in that it differs from the reference product in terms of:

- Pharmaceutical form, and
- Concentration of active substance.

As a result, this application has therefore been submitted in accordance with Article 13(3) of Directive 2001/82/EC, as amended (a hybrid generic application) which prescribes that "the results of the appropriate safety and residue tests and pre-clinical tests or clinical trials shall be provided." Notwithstanding the differences between RevitaCAM and the reference product Metacam, the applicant has conducted a comparative bioavailability study in dogs to demonstrate bioequivalence between RevitaCAM 5 mg/ml oromucosal spray and the reference product Metacam 1.5 mg/ml oral suspension.

Pharmacodynamics

No data on pharmacodynamics are presented. It is claimed that bioequivalence with the authorised reference product, Metacam 1.5 mg/ml oral suspension, has been demonstrated; therefore, cross reference to the pre-clinical studies of the reference product can be made.

Pharmacokinetics

The applicant has conducted a comparative bioavailability study in dogs to demonstrate bioequivalence between RevitaCAM 5 mg/ml oromucosal spray and the reference product, Metacam 1.5 mg/ml oral suspension. This study is reported on in Part 4 of this assessment report.

Toxicological studies

No data on basic toxicology are presented. It is claimed that bioequivalence with the authorised reference product, Metacam 1.5 mg/ml oral suspension, has been demonstrated; therefore, cross reference to the safety studies of the reference product can be made.

A target animal safety study using the final formulation was conducted. A report and comment on this study is presented in Part 4 of this assessment report.

Studies of other effects

The applicant conducted studies to determine the skin and eye irritation and the skin sensitisation potential of RevitaCAM. Based on the findings of these studies (all three studies produced negative results), it is accepted that RevitaCAM is a non-irritant and non-sensitising product.

User safety

The applicant has presented a User Safety Risk Assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/543/03-FINAL and addresses the exposure arising from the administration of the product via a pump spray.

Tasks and Situations that Lead to Exposure

RevitaCAM will be prescribed by veterinarians or suitably qualified persons, however it is expected that the product will be administered principally by the pet owner. The most likely exposure route will be dermal exposure at the time of product administration to the animal. Such exposure may occur repeatedly. Dermal, oral, ocular or inhalation exposure due to inadvertent spraying onto skin/face is considered possible, but is only likely to be as a single event. It is accepted that the product should be kept out of reach and sight of children, but there is the possibility that a child may get access to the product.

Exposure scenarios considered

- Exposure when priming the pump
- Exposure whilst administering the product to the animal
- Exposure whilst wiping the nozzle of the spray
- Exposure to the product by a non-professional user: Family member, child 15 kg

Hazard Identification and Characterisation

Information on the toxicity of meloxicam is taken from the EMEA/CVMP MRL Summary Report for that substance. The CVMP regarded a segment III reproductive study conducted in Sprague Dawley rats as the most sensitive endpoint. Based on this study, the CVMP established a LOEL of 0.125 mg/kg from which the ADI was derived. It is noted that the effect observed at 0.125 mg/kg (marginal effect on length of gestation) is considered to be of no biological importance. The LOEL of 0.125 mg/kg was used in the margin of exposure calculations.

Calculation of MOEs for meloxicam

For the various scenarios considered by the applicant, MOEs less than one have been calculated indicating a potential risk. Notwithstanding the low MOE values, the applicant argues that the actual risk is small. The CVMP accepts that the one-off exposure scenarios are not likely to be a risk to the user in terms of potential systemic effects: comparing the exposure to an end-point derived from a repeat-dose study over-estimates the risk.

Given that the user will be required to hold back the lips of the dog with one hand and administer the product with the other, the potential for dermal exposure arises each time the animal is treated. The applicant assumes that, at worst, the user may come into contact via the dermal route with 20% of the contents of each spray application. No data have been provided to substantiate this figure. However, while one-off exposure in excess of 20% may occur from time to time, it is considered highly unlikely that a user responsible for repeated administration of the product will repeatedly expose themselves to quantities of product in excess of 20% of the dose to be administered.

Regarding data on dermal absorption, the applicant refers to the CVMP EPAR for Metacam where it is stated that dermal absorption of meloxicam was 5 to 30% of that absorbed orally. The value of 30% was determined in a rabbit study and is accepted as a worst-case. In another report, in dogs, bioavailability of meloxicam from a topical gel was found to be 1.05% of that systemically available following oral administration. Dermal flux data from humans indicate that the rate of penetration of meloxicam in human skin is low. Based on all dermal absorption data presented, it can be assumed that dermal absorption in humans will be less than 30%.

In view of the above, MOE calculations were performed using the potential worst-case dermal exposure value of 20% and the potential worst-case dermal absorption value of 30%. Using these values, the worst-case exposure estimate for meloxicam is 5.38 μg/kg for a 60 kg person. When this exposure estimate is compared to the CVMP established LOEL of 0.125 mg/kg from which the ADI was derived, and applying a safety factor of 100, the MOE is 0.23. Therefore, for the chronic exposure scenario, the MOE is less than one which in accordance with the guideline indicates a potential risk. However, the following is noted:

- The MOE calculations are based on worst-case estimates and application of a safety factor of 100, and
- Meloxicam is used in man for the treatment of rheumatoid arthritis and osteoarthritis at a dose of 0.125 – 0.25 mg/kg/day. The worst case potential exposure associated with prolonged administration of the RevitaCAM is over 20-fold less than the lowest therapeutic dose in man.

In view of the above the product does not pose an unacceptable risk to the user.

Risk Management and Risk Communication

The following warnings for the user are considered appropriate:

> People with hypersensitivity to NSAIDs should avoid contact with the veterinary medicinal product. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
>
> Wash hands after administration of the product
> Avoid direct contact between the product and the skin, and if accidental exposure occurs wash hands immediately with soap and water.

The user safety statements proposed are aimed at reducing the potential for dermal exposure and are considered appropriate. It can be accepted that the product will not pose a risk to the user when used in accordance with the SPC.

Environmental risk assessment

The veterinary medicinal product will only be used in non-food animals and the environmental risk assessment can stop in Phase I. Based on the data provided the product is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

This application has been submitted in accordance with Article 13(3) of Directive 2001/82/EC, as amended (a hybrid generic application). The reference product is Metacam 1.5 mg/ml oral suspension. No data on pharmacodynamics or basic toxicology are presented. Bioequivalence with the authorised reference product Metacam 1.5 mg/ml oral suspension, has been demonstrated; therefore, cross reference to the safety/pre-clinical studies of the reference product can be made.

A comparative bioavailability study in dogs to demonstrate bioequivalence between RevitaCAM 5 mg/ml oromucosal spray and the reference product Metacam 1.5 mg/ml oral suspension has been conducted. A target animal safety study using the final formulation was also conducted. Both of these studies are presented and commented on in Part 4 of this report.

The applicant has presented a User Safety Risk Assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/543/03-FINAL. The user safety statements proposed are aimed at reducing the potential for dermal exposure and are considered appropriate. It can be accepted that the product will not pose a risk to the user when used in accordance with the SPC.

The product is not expected to pose a risk for the environment when used according to the SPC.

Residues documentation

Not applicable.

Part 4 – Efficacy

Pharmacodynamics

No data on pharmacodynamics are presented. It is claimed that bioequivalence with the authorised reference product, Metacam 1.5 mg/ml oral suspension, has been demonstrated; therefore, cross reference to the pre-clinical studies of the reference product can be made.

Development of resistance

Not applicable.

Pharmacokinetics

The applicant has conducted a single comparative bioavailability study using meloxicam oral spray 0.5% to demonstrate bioequivalence with the reference product Metacam 1.5 mg/ml oral suspension.

The study was a two-way crossover comparative pharmacokinetic study incorporating two treatments and two periods with a wash-out interval of 21 days. Twenty non-pregnant female beagle dogs were administered the test and reference products at a dose of 2 mg to each study animal (approximately 0.18 to 0.2 mg/kg given the bodyweight of animals included in the study). Blood samples were collected at appropriate time points post treatment administration into heparinised containers which were frozen to -70 ^{O}C pending analysis.

Analysis of plasma meloxicam levels was performed using a validated LC-MS/MS analytical method. Pharmacokinetic parameters were calculated using non-compartmental modeling based on time/concentration curves for meloxicam for each study animal. C_{max}, T_{max} t_{last}, and C_{last} were based on observed values whilst K_e (the elimination rate), AUC_{last} and AUC_{inf} were derived by calculations. Analysis of Variance (ANOVA) is a statistical test used to determine if more than two population means are equal. ANOVA was performed using sequence (group), period and formulation as fixed effects and animals within sequence as a random effect. Bioequivalence using the narrower confidence intervals of 80 – 125% for both C_{max} and AUC_{last} was specified *a priori*.

Bioequivalence of meloxicam oral spray 0.5% with the reference product Metacam 1.5 mg/ml oral suspension was demonstrated in terms of the pivotal pharmacokinetic parameters C_{max} and AUC_{last}. It can be accepted from the findings of this study that meloxicam oral spray 0.5% is bioequivalent to the

reference product Metacam 1.5 mg/ml oral suspension when administered on a single occasion to dogs at a dose rate of 0.2 mg meloxicam per kg bodyweight. Therefore, the absence of further pre-clinical data can be accepted.

The applicant has provided a GLP compliant validation study report on the bioanalytical method used to determine meloxicam concentrations in canine plasma. Based upon the data provided, it can be accepted that the analytical method for determining meloxicam concentrations in canine plasma has been adequately validated.

In the bioequivalence study, no adverse observations were recorded in respect of dose site irritancy. However, there were numerous observations reported following administration of the test article. The effects reported were head shaking, salivation, licking and/or chewing. In the study report, it is stated that the spray may have been less palatable than the liquid (control product) or that the novel delivery to the gums/buccal mucosa caused an unusual sensation for the animals. The fact that there may be issues in respect of palatability/unusual sensation raises questions about the use of the product (in a novel delivery system) in the field. In order to address this aspect of target animal tolerance, the applicant presented the findings of a study that reported on the ease of administration and receptiveness of the animal to the administration of the proposed pump spray delivery method of RevitaCAM.

Dose determination / justification

No data provided.

Given the legal basis of the application (Article 13(3) – a generic hybrid) and the fact that bioequivalence has been shown with the reference product on the basis of an *in vivo* comparative bioavailability study, the absence of dose determination / confirmation / justification studies can be accepted.

The proposed posology is identical to that of the reference product with which bioequivalence is shown, namely; an initial dose of 0.2 mg/kg on the first day to be continued once daily at 24 hour intervals at a maintenance dose of 0.1 mg/kg.

Further, the same advice in respect of long term treatment with the product as approved for the reference product is proposed for RevitaCAM in the SPC. *"For longer term treatment, once a clinical response has been observed (after ≥ 4 days), the dose of the product can be adjusted to the lowest effective individual dose reflecting that the degree of pain and inflammation associated with chronic musculo-skeletal disorders may vary over time."*

Given the fixed delivery volumes (50 µl, 100 µl or 215 µl) of the pump spray delivery method, titration of the dose is not possible as for other established methods of oral administration of suspensions or solutions (e.g. dosing syringe delivery). Instead, the applicant has proposed the inclusion of a dosage table with recommended dose volumes based upon bodyweight ranges. The resulting maintenance dose range of meloxicam (0.07 – 0.15 mg/kg) is in line with that approved for other fixed dosage formulations and can therefore be accepted.

Target animal tolerance

In support of the tolerance of the product, the applicant has conducted a single GLP compliant target animal tolerance study in dogs. This was a blinded and randomised controlled parallel study. 40 dogs were selected for the study (20 males and 20 females) aged approximately 9.5 to 16 months and in the bodyweight range 6.6 to 13.2 kg at the time of first treatment administration.

Animals were stratified by bodyweight within gender and randomly assigned to one of five treatment groups as shown in the table below.

The minimum treatment dose administered was 0.12 mg/kg. Treatment was administered once daily for 188 days with food being offered 1 hour after treatment administration. Physical examinations, blood analysis (haematological and biochemical) and urinalysis along with buccal mucosal bleeding time measurements were performed at appropriate intervals. Gastro-duodenal endoscopy was also performed. All dogs were euthanased at the end of the study and post mortem and histopathological examinations were conducted.

Group	Animals	Article administered	Administered dose compared to RTD	Dose of meloxicam (mg/kg)
T0	4 males and 4 females	Water (volume = 5x)	-	0
T1	4 males and 4 females	Meloxicam Spray	1x	0.12 – 0.18
T2	4 males and 4 females	Meloxicam Spray	2x	0.24 – 0.30
T3	4 males and 4 females	Meloxicam Spray	3x	0.36 – 0.43
T5	4 males and 4 females	Meloxicam Spray	5x	0.60 – 0.66

The administration of the test product to dogs for 26 weeks at 1x, 2x, 3x and 5x the high end of the proposed label dose was found to be well tolerated:

- As to be expected for an active substance belonging to the NSAID class of anti-inflammatory, the most common clinical findings were in respect of loose faeces, changes in faecal consistency, vomiting and faecal blood. It was reported that there is an increase in incidence of adverse effects in treated groups compared to controls. However, the data presented do not appear to support that conclusion in that there is no clear dose response.
- Whilst two animals showed evidence of an inflamed tongue (2x group (n=1) and 5x group (n=1)), given the low occurrence and lack of a dose relationship, such findings are not considered to be test article related.
- Whilst treatment effects were observed for some clinicopathological parameters at various time points, no persistent, dose-dependent, treatment related effect was evident. While albumin and albumin/globulin ratio appeared to decrease with increasing doses of the test article early in the treatment period, these effects resolved by day 140. It can be accepted that the changes observed are either in line with those expected for this class of anti-inflammatory drug or are of limited clinical significance.
- Median gastro-duodenal endoscopic scores for animals in study groups T1, T2, T3 and T5 were no greater (worse) than scores for animals in the control group at the final examination time point (26 weeks).
- At necropsy, no lesions of pathological significance were found in the 0x and 5x treatment groups.

It is indicated in the study that some animals were not administered the intended dose of meloxicam due to pump failure: the incidence of pump failures per treatment group ranged from 0.07% to 0.33%.

To provide further reassurances in respect of the reliability of the novel delivery system (pump spray), the applicant has provided a summary of the findings of a recently conducted controlled field study (conducted in the USA) involving 280 dogs. It would appear from the newly conducted study that only two animal owners reported issues concerning the functioning of the pump (one owner experiencing difficulty on 16 separate occasions).

It can be accepted that in general, under field conditions of use, functioning of the delivery system (pump spray) would not appear to be an issue except in isolated instances. The applicant has proposed text to be introduced into section 4.9 of the SPC in order to address the issue of possible 'pump failures' and this is considered appropriate.

Field Trials

Given that bioequivalence with the reference product has been demonstrated, it is expected that the RevitaCAM 5 mg/ml oromucosal spray will be as efficacious as the reference product Metacam 1.5 mg/ml oral suspension.

During the assessment procedure, the applicant provided a summary of the findings of a recently conducted field study entitled 'Placebo-Controlled Field Efficacy Trial of Meloxicam Administered Orally Via Transmucosal Oral Mist (Promist Technology) in Client-Owned Dogs With Osteoarthritis'. The results of this study support the ease of administration of the product and provide satisfactory evidence that administration of the product using the pump spray delivery method is generally well tolerated.

Overall conclusion on efficacy

The applicant has conducted a GLP compliant comparative bioavailability study which demonstrates that the test article meloxicam oral spray 0.5% is bioequivalent with the reference product Metacam 1.5 mg/ml oral suspension. Therefore, the absence of further pre-clinical data can be accepted.

The applicant has provided the results of a target animal tolerance study which suggest that the product should be well tolerated when administered in accordance with the recommendations proposed in the SPC. An additional study has been conducted to investigate the efficacy of the product in a placebo-controlled field trial. The results of this study support the ease of administration of the product and provide satisfactory evidence that administration of the product using the pump spray delivery method is generally well tolerated.

Part 5 – Benefit risk assessment

Benefit assessment

This application concerns a meloxicam containing product intended to be administered orally by means of a pump spray. The concentration of meloxicam is 5 mg/ml. The product is intended to be marketed with three pump delivery volumes – 50 µl, 100 µl and 215 µl delivering 0.25 mg, 0.5 mg and 1.075 mg of meloxicam respectively. It is proposed that the product is administered by directing the spray caudally and towards the gingival and/or buccal mucosal surfaces. The product is intended for both short and long term treatment of inflammation and pain in dogs associated with musculo-skeletal disorders.

Direct benefits

Given the nature of the active substance (a NSAID) it is expected that the product will provide alleviation of inflammation and pain when administered to the intended target species (dogs).

Indirect or additional benefits

Indirect benefits include a novel means of product administration of this active substance (in a pump spray) to the oromucosal surface.

Risk assessment

Possible risks to the animal following administration of the product include

- gastrointestinal irritation and/or haemorrhage
- hypersensitivity reactions to either the active substance or any of the excipients
- toxicity if administered concurrently with other NSAIDs or corticosteroids, diuretics, anticoagulants, aminoglycoside antimicrobials and substances with high protein binding effects.

It is considered that there may be a potential risk from using the product in the following animals:

- animals less than 6 weeks of age
- pregnant or lactating animals
- animals suffering from gastrointestinal disorders
- animals with impaired hepatic, cardiac or renal function
- animals with haemorrhagic disorders
- animals previously administered anti-inflammatory drugs

It is considered that there may be a potential risk from using the product in the following users:

- people with known hypersensitivity to NSAIDs.

Evaluation of the benefit risk balance

Identical warnings in respect of target animal and environmental safety are proposed for inclusion in the SPC as included in the SPC of the reference product.

The risks to the user are considered to be acceptable. The risks to the environment are not considered to be any greater than those that exist for the reference product.

Adequate data have been presented in support of quality, safety and efficacy. The benefit-risk balance can be considered positive.

Conclusion

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Directive 2001/82/EC.