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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

Scientific Discussion post-authorisation update for Loxicom extension X/003

Scope of extension: addition of 20 mg/ml solution for injection for cattle, pigs and horses

Introduction

An application for an extension of a Community marketing authorisation of Loxicom has been submitted to the European Medicines Agency (the Agency) on 30 April 2010 by Norbrook Laboratories Limited in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I thereof.

The active substance of Loxicom is meloxicam, an anti-inflammatory and antirheumatic product, non-steroids (oxicams) ATC vet code: QM01AC06.

Loxicom is currently authorised as an oral suspension and solution for injection for dogs and cats. The new extension concerns a solution for injection for cattle, pigs and horses.

The proposed indications are identical to those included in the SPC of the reference product Metacam 20 mg/ml Solution for Injection for cattle, pigs and horses, namely;

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 adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy.

Pigs: For use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation.
For adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy.

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Horses: For use in the alleviation of inflammation and relief of pain in both acute and chronic musculoskeletal disorders.
For the relief of pain associated with equine colic.

Loxicom 20 mg/ml solution for injection for cattle, pigs and horses is presented in vials of 30 ml, 50 ml, 100 ml and 250 ml. The routes of administration are subcutaneous, intramuscular or intravenous injection. The target species are cattle, horses and pigs.

Part 1 - Administrative particulars

The description of Norbrook Laboratories Limited's detailed pharmacovigilance system (DDPS) fulfils the current legal requirements. Relevant details were provided on the manufacturing sites.

Part 2 - Quality

Composition

Loxicom 20 mg/ml solution for injection contains 20 mg/ml of meloxicam as active ingredient and ethanol as antimicrobial preservative.

Container

Loxicom 20 mg/ml solution for injection in cattle, pigs and horses is presented in Type I clear glass vials, closed with bromobutyl bungs and aluminium caps. Pack sizes are 30 ml, 50 ml, 100 ml and 250 ml.

Development pharmaceutics

Loxicom 20 mg/ml solution for injection for cattle, pigs and horses has been formulated to be "bioequivalent" to the reference product Metacam 20 mg/ml solution for injection for cattle, pigs and horses. No bioequivalence studies were presented.

Method of manufacture

Manufacturing formulae for a batch range of 400 l and 4000 l batch sizes are presented. The manufacturing process is a simple standard process involving sequential addition and mixing of the excipients and active in water for injections. Process validation on two 400 l batches of the product is provided. All proposed vial sizes are represented among the vials filled from each of these batches. In general, the process can be considered to be well validated for this batch size (400 l). A commitment that additional validation on larger scale batches will be carried out in support of the larger batch size(s) has been provided.

Control of starting materials

Active substance

The active substance, meloxicam is described in the European Pharmacopoeia (Ph. Eur.). Data for meloxicam were submitted in an Active Substance Master File which has been assessed for

previous applications for Loxicom 5.0 mg/ml Solution for Injection, Loxicom 0.5 mg/ml Oral Suspension and Loxicom 1.5 mg/ml Oral Suspension.

Excipients

All product excipients comply with their respective Ph. Eur. Monograph.

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

A TSE declaration (Format 3) for the finished product is included in the dossier; all product ingredients are sourced from non-animal origin.

Control tests during production

Not applicable.

Control tests on the finished product

The specifications proposed at release and shelf-life are considered appropriate to control the quality of the finished product. Test methods for identification and quantitative determination of meloxicam and related substances and the determination of the preservative are described and are accompanied by validation data. Similarly validation data for the test for sterility and the bacterial endotoxins test have been provided.

Batch analytical data has been provided for two 400 l batches and for some developmental batches.

Stability

Finished product stability data is presented for developmental and 2 production scale batches (400 l) packaged as proposed for marketing which were stored at 25° C/60%RH for up to 12 months and 40° C/75%RH for 6 months.

The applicant proposes a shelf life of 2 years for the finished product. On the basis of the stability data presented, this proposed shelf life is considered to be acceptable by extrapolation given that satisfactory long-term data to 12 months has been provided and is accompanied by satisfactory accelerated stability data to 6 months. No special storage conditions are required and none are proposed on the SPC.

In-use stability

An in-use stability report for two batches of product packaged in the largest of the proposed vial sizes (100 ml and 250 ml) is presented. The study was conducted on recently manufactured and aged batches (12 and 24 months). The 100 ml vials were subjected to 100 broachings and the 250 ml vials were subjected to 250 broachings. Nonetheless, it is noted in the report that the number of broachings permissible for this product would be limited to that applied during the self sealing studies irrespective of the number of broachings carried out during in-use stability studies. The in-use stability study was continued for 28 days and all results for testing of physico-chemical parameters were within specification. Preservative efficacy testing was also conducted during the in-use study and demonstrates compliance with 'A' Criteria for parenteral preparations in Ph. Eur. 5.1.3.

Photostability studies show that no photo-degradation of the active substance takes place. The clear glass packaging is considered to be appropriate for the finished product and a storage precaution relating to the protection of the product from light is not required.

Overall conclusions on quality

The data provided in Part 2 of the dossier is generally in line with current guidelines. The product is generic medicinal product of a reference medicinal product (*Metacam 20 mg/ml solution for injection*) as authorised by the Community. The qualitative and quantitative composition of the product is the same as the reference product with respect to active substance and preservative. Excipients in the formulation are commonly used in veterinary medicinal products and comply with their respective Ph. Eur. monographs. The active substance is monographed in the Ph. Eur. and an ASMF demonstrating compliance is provided. The release and shelf life specifications are generally satisfactory and methods appropriately validated. Stability data to support a retest period for the active substance and a shelf life for the finished product are provided; no specific storage precautions are required for the product.

Part 3 – Safety

This application has been submitted in accordance with Article 13.1 of Directive 2001/82/EC, as amended (a generic application). .

The applicant has demonstrated that the test and reference products are bioequivalent in cattle and pigs following administration of the product by the subcutaneous and intramuscular routes respectively (data presented and commented on in Part 4 of this report). An exemption from the requirement to demonstrate bioequivalence between the test and reference products following the intravenous route of administration in cattle and horses has been justified.

In line with Article 13.1 which states 'The applicant shall not be required to provide the results of the safety and residue tests or of the pre-clinical and clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product' the absence of toxicological data is accepted.

A user safety assessment was provided by the applicant. While the assessment was not conducted in accordance with the CVMP user safety guideline, it can be accepted that the risk to the user posed by the test product will be similar to that posed by the reference product. Consequently, the user safety statements approved for the reference product can be applied to the test product. The following user safety statements are proposed:

- Accidental self injection may cause pain.
- People with known hypersensitivity to non-steroidal anti-inflammatory drugs (NSAID) should avoid contact with the veterinary medicinal product.
- In case of accidental self-injection, seek medical advice immediately and show the package leaflet or label to the physician.

The applicant has provided an environmental risk assessment in accordance with the VICH GL6, Guideline on Phase I environmental impact assessments. Given that the product (a NSAID) is intended to be used to treat a small number of animals in a flock or herd, the CVMP has concluded that the phase I assessment can stop at question number 5 with respect to all the intended target species (cattle, pigs and horses). The CVMP considers the environmental risk assessment for Loxicom to be satisfactory.

Residues documentation

In support of the application, the applicant has conducted two *in-vivo* bioequivalence studies (one in cattle following subcutaneous administration and one in pigs following intramuscular administration) confirming that the test product Meloxicam (Loxicom) 20 mg/ml and the reference product Metacam 20 mg/ml are bioequivalent.

Title III of Annex I to Directive 2001/82/EC as amended, indicates that evidence to demonstrate equivalent or differing depletion of residues from the administration site only is required for generic veterinary medicinal products intended to be administered by the intramuscular, subcutaneous or transdermal routes. Therefore, the applicant has conducted two injection site residue depletion studies using the test product (Meloxicam (Loxicom) 20 mg/ml) – one in cattle following the subcutaneous administration and the other in pigs following the intramuscular administration.

In accordance with the 'alternative' approach for the setting of withdrawal periods, an appropriate withdrawal period is based on the first time point at which all tissue samples were demonstrated to have residue concentrations below the relevant MRL plus an additional safety factor (typically 10-30%) to account for variability. For cattle, the first time point at which all tissue samples were demonstrated to have meloxicam residue concentrations below the muscle MRL (20 µg/kg) was at the 10 day slaughter time point. Therefore, the withdrawal period proposed by the applicant for subcutaneous administration in cattle (15 days) includes an additional safety span of 50%.

For pigs, the first time point at which all tissue samples were demonstrated to have meloxicam residue concentrations below the muscle MRL (20 µg/kg) was at the Day 3 slaughter time point. The withdrawal period proposed by the applicant following intramuscular administration of the product in pigs (5 days) includes a safety span of 66%.

With regard to the intravenous route of administration in cattle and horses, an exemption from the requirement to demonstrate bioequivalence with the reference product in line with section 4(a) of the CVMP bioequivalence guideline applies. Furthermore, title III of Annex I to Directive 2001/82/EC as amended indicates that evidence to demonstrate equivalent or differing depletion of residues from the administration site are only required for generic veterinary medicinal products intended to be administered by the intramuscular, subcutaneous or transdermal routes. In accordance with the above, the omission of residue data in respect of the intravenous administration of Meloxicam (Loxicom) 20 mg/ml to horses and cattle can be accepted.

In conclusion, based on the data provided, it can be accepted that the withdrawal periods approved for the reference product Metacam 20 mg/ml are applicable to the test product Meloxicam (Loxicom) 20 mg/ml solution for injection. These are:

Cattle:

Meat and offal: 15 days

Milk: 5 days

Pigs:

Meat and offal: 5 days

Horses:

Meat and offal: 5 days.

Part 4 – Efficacy

This application has been submitted in accordance with Article 13.1 of Directive 2001/82/EC, as amended (a generic application). In support of the application, the applicant has conducted two *in vivo* bioequivalence studies, one in cattle following subcutaneous administration and one in pigs following intramuscular administration. Based on the findings of these studies, it is accepted that the test product Loxicom (Meloxicam) 20 mg/ml and the reference product Metacam 20 mg/ml are bioequivalent.

The product is also indicated for administration using the intravenous route in both horses and cattle. The justification for the omission of *in vivo* bioequivalence studies in horses and cattle following administration of the test product using the intravenous route can be accepted as the exemption claimed meets the criteria prescribed in section 4(a) of the CVMP bioequivalence guideline which states 'The product is a solution intended solely for intravenous administration and contains the same active substance or therapeutic moiety as an intravenous solution approved for use in the target species which is the subject of the new application'.

Notwithstanding the limitations in terms of animal numbers, the target animal tolerance studies conducted by the applicant demonstrate that the test product was well tolerated following administration to cattle using the subcutaneous route and to pigs using the intramuscular route at doses up to 5 X RTD and for a period of three times the recommended treatment duration.

Furthermore, target animal tolerance was investigated in both cattle and horses following the intravenous administration of the product. Whilst the design of these studies was not in accordance with the recommendations prescribed in the VICH GL43 guideline on target animal safety for veterinary medicinal products (EMEA/CVMP/VICH/393388/2006) in terms of animal numbers, treatment durations nor doses investigated, it can be accepted that the test product was well tolerated following intravenous administration to cattle and horses at the recommended treatment dose and for a period of twice the recommended treatment duration.

No data have been provided by the applicant in respect of dose determination/justification, dose confirmation or field trials. In line with Article 13.1 which states 'The applicant shall not be required to provide the results of the safety and residue tests or of the pre-clinical and clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product.' The absence of pre-clinical/clinical trials is accepted.

Part 5 – Benefit risk assessment

The application for Loxicom 20 mg/ml solution for injection for cattle, pigs and horses is a generic application and is submitted in accordance with Article 13.1 of Directive 2001/82/EC as amended.

Loxicom 20 mg/ml solution for injection for cattle, pigs and horses contain meloxicam as active ingredient. The product was developed in such a way as to closely resemble the formulation of the originator product, Metacam 20 mg/ml solution for injection for use in cattle, pigs and horses.

The indications are the same as for the reference product, namely the reduction of clinical signs associated with respiratory disease in cattle, diarrhoea in calves and young non-lactating cattle and acute mastitis in cattle, non-infectious locomotor disorders in pigs, puerperal septicaemia and toxaemia in sows and acute and chronic musculoskeletal disorders in horses.

The active substance, meloxicam, is a well known non-steroidal anti-inflammatory drug in veterinary medicine. It has been included in other formulations of Loxicom which have already been authorised as oral suspensions for dogs and cats and solutions for injection for dogs and cats.

The primary mode of action of meloxicam is inhibition of cyclo-oxygenases in the arachidonic acid inflammatory pathway. It is beneficial in animal welfare and aid in the control of inflammatory symptoms associated with the disorders specified in section 4.2 of the SPC.

The reduction in severity of illness in the above conditions may be considered as an additional positive benefit in respect of improved herd productivity.

Given the nature of the application (a generic), the applicant has demonstrated bioequivalence between the test and reference products following the subcutaneous and intramuscular administration in cattle and pigs respectively. In addition, the applicant has justified an exemption from the requirement to demonstrate bioequivalence between the test and reference products following intravenous administration in cattle and horses in accordance with paragraph 4 (a) of the bioequivalence guidelines. The CVMP considered that risks identified for this product are strictly the same as those for the reference product. No negative impact on the environment is anticipated. Appropriate information and warnings are included in the SPC and product information to prevent risks for the animals, the user and for the environment.

The overall benefit risk balance is deemed positive.

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 as amended.