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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/005

### Scope of extension: addition of 1 mg and 2.5 mg chewable tablets for dogs

## 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, a non-steroidal (oxicam), anti-inflammatory and antirheumatic drug, ATC vet code: QM01AC06.

Loxicom is currently authorised as oral suspensions and solutions for injection for dogs and cats and as a solution for injection for cattle, pigs and horses. The new extension concerns chewable tablets for dogs.

The proposed indications are identical to those included in the SPC of the reference product Metacam 1 mg and 2.5 mg chewable tablets for dogs, namely the alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders.

The new presentation will be available as 1 mg/tablet and 2.5 mg/tablet and is to be administered orally. It is presented in blister packs of 10 tablets per strip in cartons containing 10, 20, 100 or 500 tablets.

## 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.

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# Part 2 - Quality

## *Composition*

Loxicom 1 mg and 2.5 mg chewable tablets for dogs contain meloxicam as active ingredient. Various excipients are present in the formulation which can be considered 'standard' excipients that are commonly used in veterinary medicinal products.

## *Container*

The product is to be packaged in blister packs composed of PVC/PVDC base foil and aluminium lidding foil of 10 tablets in presentations of 10, 20, 100 and 500 tablets.

## *Development Pharmaceutics*

In line with the reference product Metacam 1 mg and 2.5 mg chewable tablets for dogs, the generic product contains the active substance meloxicam at concentrations of 1 mg/tablet and 2.5 mg/tablet. The excipients of Loxicom chewable tablets for dogs differ from those of the reference product Metacam chewable tablets for dogs. Those differences are considered acceptable.

Not all excipients are of pharmacopoeial grade, but they are standard excipients commonly used in veterinary medicinal products with the exception of the combination of microcrystalline cellulose with guar gum. Microcrystalline cellulose is a widely used excipient and guar gum is used in a number of authorised medicinal products. Both comply with their respective European Pharmacopoeia (Ph. Eur.) and United States Pharmacopeia (USP) monographs. Comparative dissolution tests were performed between each strength of the proposed tablets which indicate similar release profiles between each strength. Comparative dissolution between the 2.5 mg tablet and the reference product Metacam chewable tablets 1 mg and 2.5 mg and Metacam 1.5 mg/ml oral suspension have also been conducted and similar profiles demonstrated.

Each tablet contains a break line and compliance with the Ph. Eur. requirements for subdivision of tablets has been shown.

## *Method of manufacture*

The tablets are manufactured using standard wet granulation manufacturing processes and both tablet strengths are produced from a common blend. The manufacturing process is well described. Comprehensive validation of the manufacturing process for each tablet strength has been conducted and it was shown that the manufacturing process itself does not induce degradation of the active substance as no increase in degradation products is observed following manufacture.

## *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. A 24 month re-test period for meloxicam was accepted during those procedures and is also applicable for this procedure.

The active substance complies with the Ph. Eur. monograph for meloxicam.

## Excipients

Pharmacopoeial excipients comply with their respective Ph. Eur. monographs.

Several excipients are used in the formulation which are not described in a pharmacopoeia. Adequate information was provided regarding the qualitative and quantitative composition of these excipients and this is considered acceptable.

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

A declaration is provided by the active substance supplier that meloxicam does not contain, or use during manufacture, any materials of bovine, ovine or caprine origin. Further, appropriate declarations are provided for the excipients. The TSE status of the product was considered to be adequately demonstrated and is acceptable.

## *Control tests on the finished product*

The specification proposed at release is considered appropriate to control the quality of the finished product. Test methods for identification and quantitative determination of meloxicam and related substances are described and are accompanied by validation data. Other standard analytical methods are also described. Batch analytical data have been provided and they are accepted as the results are all in compliance with the appropriate limits.

Information on the reference material utilised during analysis of the finished product is presented.

## *Stability*

Finished product stability data is presented for 3 batches of the common blend which was compressed into both tablet strenghts. Stability batches were packaged as proposed for marketing and stored at 25 °C/60%RH and 40 °C/75%RH.

The Committee agreed that based on the data currently available, a shelf life of 18 months with a storage precaution of 'Do not store above 25 °C' is considered appropriate for the product. Instructions to store in the original package in order to protect from light are also appropriate.

The applicant has confirmed that the first 3 post-approval production batches will be placed on stability.

Short term in-use stability data for half tablets are provided in the dossier which demonstrate they may be stored for 24 hours prior to use.

## *Overall conclusion on quality*

The different composition of Loxicom chewable tablets in terms of the excipients in comparison to the reference product was considered to be acceptable. The manufacturing process is a standard one and adequate process validation data are presented in the dossier. Specifications for the active substance and the excipients are satisfactory and in compliance with appropriate pharmacopoeia monographs where applicable or are standard excipients commonly used in veterinary products. The release and shelf life specifications are considered acceptable to ensure the quality of the product at release and for the duration of its shelf life. Analytical methods have been presented and validated in accordance with VICH requirements.

Stability studies are presented in the dossier and support a shelf life of 18 months when stored below 25 °C. Half tablets may be stored for 24 hours prior to use.

# Part 3 – Safety

This application has been submitted as an extension application to introduce a new pharmaceutical form, namely chewable tablets.

No data on the toxicological, mutagenic and carcinogenic properties of the product were provided.

As bioequivalence was demonstrated between Loxicom chewable tablets and the reference product (Metacam 1 mg and 2.5 mg chewable tablets for dogs) by in *vivo* bioavailability studies as described in Part 4 of this report, the omission of those data can be accepted.

An overview of the characteristics and uses of the excipients included in the proposed formulation were provided. Those excipients not included in the reference product (according to the published SPCs) are commonly used in either the pharmaceutical industry or the food manufacturing industry.

Based on the user safety assessment provided, it can be accepted that the risk to the user posed by Loxicom 1 mg and 2.5 mg chewable tablets for dogs will be similar to that posed by the reference product Metacam 1 mg and 2.5 mg chewable tablets for dogs. Consequently, the user safety statements approved for the reference product can be considered appropriate for Loxicom chewable tablets.

As the product is intended for the treatment of non-food animals, the environmental risk assessment can end at Phase I. When used as recommended, the product will not pose a risk to the environment. The same disposal advice is proposed for inclusion in the SPC as is approved for the reference products.

# Part 4 – Efficacy

In support of the application, two *in vivo* bioavailability studies were conducted in order to investigate the pharmacokinetic profile of the active substance and to demonstrate bioequivalence. One is a comparative bioavailability study between the test product Loxicom 2.5 mg chewable tablets for dogs and the product Metacam 1.5 mg/ml oral suspension for dogs, the other is a comparative bioavailability study between the test product Loxicom 2.5 mg chewable tablets for dogs and the reference product Metacam 2.5 mg chewable tablets for dogs. From the data presented, bioequivalence of Loxicom 2.5 mg chewable tablets with the cited reference product, Metacam chewable tablets for dogs, was shown.

In order to demonstrate bioequivalence between Loxicom chewable tablets and the reference product in respect of the lower strength of tablets (1 mg) an *in vitro* dissolution study was performed comparing Loxicom 2.5 mg chewable tablet with Loxicom 1 mg chewable tablet. It was shown that the lower strength tablet has a similar dissolution profile in comparison to the higher strength Loxicom 2.5 mg tablet. Therefore the *in vivo* bioequivalence between Loxicom 1 mg chewable tablet and the reference product Metacam 1 mg chewable tablet can be concluded.

Given that this product is a generic medicinal product and that the applicant has demonstrated bioequivalence with the reference product (Metacam 1 mg and 2.5 mg chewable tablets for dogs), the omission of clinical efficacy studies was accepted. It can be concluded that the efficacy profile for the Loxicom chewable tablets and the reference product will be comparable.

In support of the extension application for 1 mg and 2.5 mg chewable tablets for dogs a target animal safety study was presented which gives some assurances regarding the safety of the product. The product was well tolerated when administered at a dose of up to 3 times the recommended treatment dose for a period of up to 10 days. It is accepted that the safety profile of Loxicom chewable tablets will be similar to that of the authorised reference product and that the adverse effects that could

potentially be associated with the use of this product are adequately detailed in section 4.6 of the proposed SPC.

A palatability study has been conducted by the applicant and it can be accepted from the results of this study that the test product (Loxicom 1 mg chewable tablets) is at least as palatable as the reference product (Metacam 1 mg chewable tablets for dogs).

# Part 5 – Benefit risk assessment

Loxicom 1 mg and 2.5 mg chewable tablets for dogs contain meloxicam as active ingredient. The product was developed in such a way as to broadly resemble the formulation of the originator product, Metacam 1 mg and 2.5 mg chewable tablets for dogs.

The indication is the same as for the reference product, namely the alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders.

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, cats, cattle, pigs and horses.

The primary mode of action of meloxicam is inhibition of cyclo-oxygenases in the arachidonic acid inflammatory pathway. It is beneficial in the alleviation of inflammation and pain in both acute and chronic musculoskeletal disorders in a number of species, including dogs.

The availability of an orally administered tablet formulation to facilitate administration by the owner may be considered as an additional benefit.

Since bioequivalence was demonstrated *in vivo* between the products, Loxicom chewable tablets for dogs are expected to be as safe and efficacious as Metacam chewable tablets for dogs when administered at the recommended treatment dose.

The risks identified for this product are strictly the same as those that exist 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 Loxicom 1 mg and 2.5 mg chewable tablets for dogs were considered to be in accordance with the requirements of Directive 2001/82/EC as amended.