United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Milprazin 2.5 mg / 25 mg Tablets for Small Dogs and Puppies Weighing at Least 0.5 kg

Milprazin 12.5 mg / 125 mg Tablets for Dogs Weighing at Least 5 kg

Date Created: January 2018

PuAR correct as of 18/05/2018 when RMS was transferred to NL. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Milprazin 2.5 mg / 25 mg Tablets for Small Dogs and Puppies Weighing at Least 0.5 kg Milprazin 12.5 mg / 125 mg Tablets for Dogs Weighing at Least 5 kg
Applicant	KRKA d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
Active substance	Milbemycin oxime, praziquantel
ATC Vetcode	QP54AB51
Target species	Dogs Milprazin 2.5 mg / 25 mg Tablets for Small Dogs and Puppies Weighing at Least 0.5 kg Milprazin 12.5 mg/125 mg tablets for dogs weighing at least 5 kg
Indication for use	In dogs: treatment of mixed infections by adult cestodes and nematodes of the following species: - Cestodes: *Dipylidium caninum* *Taenia* spp. *Echinococcus* spp. *Mesocestoides* spp. - Nematodes: *Ancylostoma caninum* *Toxocara canis* *Toxascaris leonina* *Trichuris vulpis* *Crenosoma vulpis* (Reduction of the level of infection) *Angiostrongylus vasorum* (Reduction of the level of infection by immature adult (L5) and adult parasite stages; see specific treatment

	and disease prevention schedules under section 4.9 "Amounts to be administered and administration route") *Thelazia callipaeda* (see specific treatment schedule under SPC[1] section 4.9 "Amounts to be administered and administration route") The product can also be used in the prevention of heartworm disease (*Dirofilaria immitis*) if concomitant treatment against cestodes is indicated.

[1] SPC – Summary of Product Characteristics.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic applications in accordance with Article 13 (1) of Directive 2001/82/EC as amended.

I. SCIENTIFIC OVERVIEW

These applications were for generic products, submitted in accordance with Article 13 (1) of Directive 2001/82/EC as amended. The reference products are Milbemax Tablets for Small Dogs and Puppies and Milbemax Tablets for Dogs marketed in the UK since April 2003. The applicant has conducted a bioequivalence study between the proposed product Milprazin 12.5 mg / 125 mg Tablets for Dogs Weighing at Least 5 kg and the reference product Milbemax Tablets for Dogs. A dose proportionality based biowaiver is presented to justify the omission of a similar study with the lower strength tablet.

The products are intended for dogs, and each product is administered according to the weight of the animal. The products are intended for the treatment of mixed infections by immature and adult cestodes and nematodes.

The products are produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the products can be safely used in the target species, any reactions observed are indicated in the SPC. The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] of the products was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The products contain either 2.5 mg milbemycin oxime and 25 mg praziquantel, or 12.5 mg milbemycin oxime and 125 mg praziquantel as active substances. The excipients are cellulose microcrystalline, lactose monohydrate, povidone, croscarmellose sodium, silica colloidal anhydrous, magnesium stearate, meat flavour and yeast powder.

[2] Efficacy – The production of a desired or intended result.

12.45/125 mg product

The container/closure system consists of blister packs formed of cold formed OPA/Al/PVC foil and aluminium foil, contained within a box, with 1 blister of 2 tablets.

2.5 mg/25 mg product

The container/closure system consists of blister packs formed of cold formed OPA/Al/PVC foil and aluminium foil, contained within a box, with 1 blister of 2 tablets, or 1 blister with 4 tablets.

The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the absence of preservative are justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a simple mixing, compression and coating process. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substances are milbemycin oxime and praziquantel, established active substances. Praziquantel is monographed in the European Pharmacopoeia (Ph. Eur). Milbemycin oxime is supplied in accordance with an active substance master file, and controlled under specific specifications. The active substance is manufactured in accordance with the principles of good manufacturing practice. The active substance specification is considered

adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided. All excipients are monographed in the Ph. Eur, apart from yeast powder and meat flavour.

II.C.4. Substances of Biological Origin

Lactose monohydrate is the only substance derived from animal origin, and is derived from milk and calf rennet. The lactose monohydrate is assured as being from milk sourced from healthy animals, kept in the same conditions as cows from which milk is collected for human consumption. The lactose is prepared without the use of ruminant materials, other than calf rennet.

Individual TSE certificates for each excipient are provided confirming compliance with the Note for Guidance EMEA/410/01 rev. 3 on ‘Minimising the risk of

Transmitting Animal Spongiform Encephalopathy agents via human and veterinary medicinal products'.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Control tests on the finished product include: appearance, uniformity of mass, water content, dimensions, uniformity of dosage units, identification of the active substances and related substances and microbiological quality.

II.F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. The retest period for the active substances was established as being 24 months. Suitable tests performed under VICH recommended guidelines demonstrated that the finished product was stable as cited in the SPC.

G. Other Information

2.5 mg/25 mg product

Shelf life of the veterinary medicinal product as packaged for sale: 3 years

Shelf life for halved tablets after first opening the immediate packaging: 6 months.

Halved tablets should be stored below 25°C in the original blister and be used for the next administration.

12.45/125 mg product

Shelf life of the veterinary medicinal product as packaged for sale: 3 years

Store in the original package in order to protect from moisture. This veterinary medicinal product does not require any special temperature storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As these were generic applications according to Article 13 (1) and bioequivalence with a reference product has been demonstrated, results of pharmacological and toxicological tests are not required. The aspects of these products are identical to the reference product.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and the environment.

III.A Safety Documentation

Pharmacological Studies

The applicant stated that the product is quantatively and qualitatively similar to the reference product, and this was demonstrated. Any differences in the excipients of the proposed products and the reference products were addressed in the user risk assessment.

User Safety

A user risk assessment was provided in compliance with the relevant guideline.
A large amount of bibliographical data were submitted to support the user safety for the active substances. All excipients were regarded as safe for use at their specified levels in the products. A repeated dose study in dogs and rats demonstrated a NOEL[3] of 3 mg/kg/bw/day for milbemycin oxime. Vomiting, neurotoxicity and hypertrophy can be seen at overdose. For praziquantel, a NOEL of 33 mg/kg/bw/day was noted in the rat. Praziquantel is commonly used in human medicine and has an established safety profile. With regard to reproductive toxicity, mutagenicity, carcinogenicity, no adverse effects were noted in studies where the quantity of the active substances were within the range stipulated by the SPC. No eye or skin sensitising concerns were raised. The product is most likely to be handled by veterinary professionals or the pet owner. Warnings and precautions as listed on the product literature, which match those of the reference product, and in addition to take into account the scoring of the tablets, are adequate to ensure safety to users of the product. The products should in particular be kept out of the sight and reach of children.

- Wash hands after use.
- In the event of accidental ingestion of the tablets, particularly by a child, seek medical advice immediately and show the package leaflet or the label to the doctor.

[3] NOEL – No observed effect limit.

Environmental Safety

The effect of the products on the environment will be minimal as they will be used in individual instances, in small amounts, for companion animals. The warnings match those of the reference product:

- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

- The product should not enter water courses as this may be dangerous for fish and other aquatic organisms.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The applicant successfully claimed that the proposed products and reference product have comparatively the same composition and contain the same excipients. Therefore, no further data were required in this section.

Pharmacokinetics

The applicant has conducted an *in vivo* bioequivalence study to compare two formulations of the proposed product, Milprazin 12.5 mg/125 mg Film-Coated Tablets for Dogs weighing at least 2 kg, with the reference product, Milbemax Film-Coated Tablets for Dogs. This was a GLP[4]-compliant three-way crossover bioavailability study, at a single site. The wash-out period was at least 30 days. 24 male Beagle dogs aged between 11 and 29 months and weighing between 8.25 and 10.92 kg were clinically evaluated and acclimatised 1 week before treatment.

A single oral dose was given, and animals were observed following treatment. Blood sampling was performed at specific time points, and suitable analytical methods used to analyse the plasma levels of the active substances. Appropriate pharmacological and statistical methods of measurement were used to analyse the results of the blood tests. Bioequivalence was assessed using the 90% confidence interval of parameters, where equivalent results were expected

be seen within the acceptance range of 80 – 125% for the pharmacokinetic parameters AUC_{0-t}[5] and C_{max}[6], for one of two trial formulations tested. It was

[4] GLP – Good Laboratory Practice.
[5] AUC_{0-t} – Area under the curve, from commencement of assay to final time-point.

found on suitable investigation into relevant parameters that bioequivalence between the proposed product and the reference product was established.

In order to justify the formulation for Milprazin 2.5 mg/25 mg Film-coated Tablets for Small Dogs and Puppies weighing at 0.5 kg, in addition to claiming that the qualitative composition of the two strengths of product are the same, and that the composition of strengths is relatively proportional as stipulated in the relevant document paragraph 7 point 7.2 of EMA/CVMP/016/00-Rev.2, a suitable dissolution study was performed. This compared the 12.5/125 mg mg proposed product with the 2.5 mg/25 mg proposed product under suitable buffer

conditions, (3 pH values, pH7.4, pH 4.5, pH 1.0). Suitable statistical analysis was performed from the resulting data. It was established that bioequivalence could be inferred between the two product strengths.

Tolerance in the Target Species

As these were generic products and bioequivalence with a reference product was established, there was no need for further data in this section.

Resistance

As these were generic products and bioequivalence with a reference product was established, there was no need for further data in this section.

IV.II. Clinical Documentation

As these were generic products and bioequivalence with a reference product was established, there was no need for further data in this section.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the product(s) is favourable.

[6] C_{max} – Maximum concentration of active substance obtained.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

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The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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