Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Milquantel 4 mg/ 10 mg film-coated tablets for small cats and kittens weighing at least 0.5 kg

Date Created: July 2017

Updated: October 2017

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

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0534/001/E/001
Name, strength and pharmaceutical form	Milquantel 4 mg/ 10 mg film-coated tablets for small cats and kittens weighing at least 0.5 kg
Applicant	KRKA d.d., Novo Mesto Šmarješka Cesta 6 8501 Novo Mesto Slovenia
Active substance(s)	Milbemycin oxime Praziquantel
ATC Vetcode	QP54AB51
Target species	Cats (small cats and kittens)
Indication for use	In cats: treatment of mixed infections by immature and adult cestodes and nematodes of the following species: - Cestodes: *Dipylidium caninum* *Taenia* spp. *Echinococcus multilocularis* - Nematodes: *Ancylostoma tubaeforme* *Toxocara cati* Prevention of heartworm disease (*Dirofilaria immitis*) if concomitant treatment against cestodes is indicated.

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 application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	25th February 2015
Date of completion of current MRP procedure	24th May 2017
Concerned Member States for original procedure	First Use France Repeat Use Italy, Netherlands

I. SCIENTIFIC OVERVIEW

Milquantel 4 mg/ 10 mg film-coated tablets for small cats and kittens weighing at least 0.5 kg have been developed as generic products of Milbemax film-coated tablets for small cats and kittens. The reference product has been authorised in the UK since April 2003. Bioequivalence has been demonstrated between Milquantel film-coated tablets for cats and Milbemax film-coated tablets for cats and the dose proportionally based biowaver was presented to justify the omission of a similar study with the 4 mg presentation.

The product contains milbemycin oxime and praziquantel, which should be administered at a dose rate of 2 mg /kg and 5 mg /kg respectively. Milquantel is indicated for the treatment of mixed infestations of adult cestodes and nematodes, as well as the prevention of heartworm disease. The product is contraindicated in cats of less than six weeks of age and / or weighing less than 0.5 kg and in animals where there is a known hypersensitivity to the active substance or to any of the excipients.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC[1]. 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 product was demonstrated

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

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 product contains milbemycin oxime and praziquantel as the active substances. The excipients for the tablet core are cellulose microcrystalline, lactose monohydrate, povidone, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate. The excipients for the tablet coating are hypromellose, talc, propylene glycol, titanium dioxide (E171), meat flavour, yeast powder and iron oxide yellow (E172).

The container / closure system consists of OPA/Al/PVC foil and aluminium foil blister packs containing 2, 4 and 48 tablets packaged in a cardboard carton. The particulars of the containers and controls performed are provided and conform to the regulation.

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 product is manufactured by mixing the active substances with povidone and croscarmellose sodium before adding purified water to granulate. The remaining excipients are then mixed with the granulate and the mix is compressed into tablets, which are then packaged. 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 described in the European Pharmacopoeia (Ph. Eur.) and a Ph. Eur. Certificate of Suitability has been supplied. Milbemycin oxime is not described in a pharmacopoeia and data on the active substance have been supplied in the form of an Active Substance Master File (ASMF). The active substances are manufactured in accordance with the principals 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 of the excipients, apart from meat flavour, yeast powder and iron oxide, are described in the European Pharmacopoeia and are manufactured in accordance

with the relevant Ph. Eur. Monograph. Data were provided for the manufacture of the remaining excipients. Certificates of analysis were provided for all excipients.

II.C.4. Substances of Biological Origin

Certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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. The tests include those for identification and assay of the active substances, dissolution of the active substances, appearance and microbiological quality.

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.

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 praziquantel is 36 months as described in the Ph. Eur. Certificate of Suitability. A retest period of 24 months has been determined for milbemycin oxime.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Data were provided on batches of the finished product stored at 25°C/60% RH for 12 months and 40°C/75% RH for 6 months.

An in-use shelf life of 3 months after halving tablet is based on the demonstration of stability for a batch broached and stored at 25°C/60% RH for 6 months.

G. Other Information

Shelf life:
Shelf life of the veterinary medicinal product as packaged for sale: 3 years
Shelf life for halved tablets after first opening the immediate packaging: 3 months

Special precautions for storage:
Store in the original package in order to protect from moisture.
Halved tablets should be stored below 25°C in the original blister and be used for the next administration.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required.

Toxicological Studies

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, results of toxicological tests are not required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the most likely routes of exposure are dermal, ocular through accidental hand to eye transfer or oral, again by accidental transfer. The risk to the user is considered to be the same as for the reference product. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- 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.
- Echinococcosis represents a hazard for humans. As Echinococcosis is a notifiable disease to the World Organisation for Animal Health (OIE), specific guidelines on the treatment and follow-up, and on the safeguard of persons, need to be obtained from the relevant competent authority.

Environmental Safety

An environmental risk assessment (ERA) was provided in accordance with VICH and CVMP guidelines.

Phase I:
The ERA concluded that the product is not expected to pose a risk to the environment when used as recommended in the SPC. The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required. The product is considered to have the same pharmacodynamics particulars as the reference product.

Pharmacokinetics
An *in vivo* bioequivalence study was provided comparing Milquantel 16 mg / 40 mg film coated tablets for cats with the reference product. Bioequivalence was accepted between the test product and the reference product. As bioequivalence was demonstrated between the higher strength milbemycin oxime / praziquantel product justification for the omission of an *in vivo* bioequivalence study with Milquantel 4 mg / 10 mg film-coated tablets for small cats and kittens was accepted.

A dissolution study was provided for the 4 mg / 10 mg tablet for comparison with Milquantel 16 mg / 40 mg tablet test product. The dissolution profiles of the tablets were compared using three dissolution media at different pH; 1.0, 4.5 and 7.4. The dissolution profiles were then compared for the products, with samples taken at appropriate times.

The curves were considered to be similar if the f2 (similarity factor) value was ≥50. The results showed similar profiles for both milbemycin oxime and praziquantel for the products. The f2 values were all between 50 and 100, indicating similarity of the dissolution profiles.

Tolerance in the Target Species

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been

demonstrated, results of tolerance studies are not required. References were also supplied to demonstrate that the active substances are well tolerated by the target species. In addition, the applicant conducted an *in vivo* bioequivalence study and the test product was well tolerated by the cats in the study.

Resistance

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, resistance data are not required.

IV.II. Clinical Documentation

Laboratory Trials

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, results of laboratory trials are not required.

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.

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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