



College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

**Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands**

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: June 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0260/001
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: <i>Dipylidium caninum</i> <i>Taenia</i> spp. <i>Echinococcus multilocularis</i> - Nematodes: <i>Ancylostoma tubaeforme</i> <i>Toxocara cati</i> Prevention of heartworm disease (<i>Dirofilaria immitis</i>) if concomitant treatment against cestodes is indicated.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website:

<http://mri.medagencies.org/veterinary/>

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	25 th February 2015
Date of completion of current MRP procedure	24 th May 2017
Concerned Member States for original procedure	<u>First Use</u> France <u>Repeat Use</u> 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 SPC¹. 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 efficacy² of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

¹ SPC – Summary of product Characteristics.

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

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 and Milbemycin oxime are both described in the European Pharmacopoeia (Ph. Eur.) and Ph. Eur. Certificates of Suitability have been supplied. The active substances are 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 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 milbemyacin 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 6 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: 6 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 Milquandel 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 milbemyacin oxime / praziquantel product justification for the omission of an *in vivo* bioequivalence study with Milquandel 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 Milquandel 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 milbemyacin 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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section 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.

•	21 May 2020	Submission of a new Eur. certificate of suitability from a new manufacturer for an active substance, addition
•	19 March 2020	Extension of the shelf life of the finished product after first opening
•	13 December 2019	Renewal
•	28 June 2019	Addition of a manufacturing site for the finished product
•	28 March 2019	Submission of a new Ph. Eur. certificate of suitability for an active substance from an already approved manufacturer and update CEP
•	28 March 2019	Addition of manufacturing site for primary packaging, secondary packaging and batch control
•	14 February 2019	Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (DDPS), change in the safety database
•	19 September 2018	Change of specifications for Active substance to comply with Ph. Eur
•	18 May 2018	Change in RMS from UK to NL.
•	8 March 2018	Harmonise and finalise SPCs and QRDs after a repeat-use procedure
•	25 October 2017	Deletion of a manufacturing site of the active substance.
•	18 October 2017	Increase in the shelf-life of the finished product as packaged for sale, from 2 years to 3 years.
•	25 July 2017	Change in distributor details. Deletion of Intervet UK Ltd and addition of Alloga UK Limited, Centaur Services Limited & National Veterinary Services Limited.
•	12 June 2017	Repeat Use application to add 2 new member states
•	22 December 2016	Addition of secondary packaging site of the finished product.
•	24 August 2016	Change in test procedure for the active substance.
•	August 2016	Addition of a manufacturer of the active substance.
•	09 June 2016	Submission of a new Certificate of suitability.
•	14 October 2015	Introduction of a new pharmacovigilance system
•	10 July 2015	Change of MAH.

		Addition of distributors and a local UK representative. Approval of mock-ups.
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