Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Milbactor 2.5 mg/25 mg Tablets for Small Dogs and Puppies weighing at least 0.5 kg
Milbactor 12.5 mg/125 mg Tablets for Dogs weighing at least 5 kg

Date Created: 18th March 2015

Updated: October 2017

PuAR correct as of 27/04/2018 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0530/001/DC UK/V/0530/002/DC
Name, strength and pharmaceutical form	Milbactor 2.5 mg/25 mg Tablets for Small Dogs and Puppies weighing at least 0.5 kg Milbactor 12.5 mg/125 mg Tablets for Dogs weighing at least 5 kg
Applicant	Krka, d.d. Šmarješka cesta 6 8501 Novo mesto Slovenia
Active substance(s)	Milbemycin oxime Praziquantel
ATC Vetcode	QP54AB51
Target species	Dogs
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 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.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

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	24th September 2014
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden

I. SCIENTIFIC OVERVIEW

Milbactor Tablets for Dogs and Milbactor Tablets for Small Dogs and Puppies have been developed as generic products of Milbemax Tablets for Dogs and Milbemax Tablets for Small Dogs and Puppies. The reference products have been authorised in the UK since April 2003. Bioequivalence has been demonstrated between Milbactor Tablets for Dogs and Milbemax Tablets for Dogs. A biowaiver has been accepted for the lower tablet strength.

The products contain milbemycin oxime and praziquantel, which should be administered at a dose rate of 0.5 mg/ kg and 5 mg/kg respectively. Milbactor is indicated for the treatment of mixed infestations of adult cestodes and nematodes, as well as the prevention of heartworm disease. The products are contraindicated in animals where there is a known hypersensitivity to the active substance or 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 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 active substances. The excipients are cellulose (microcrystalline), lactose monohydrate, povidone, croscarmellose sodium, colloidal anhydrous silica, meat flavour, yeast powder and magnesium stearate.

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

The choice of the formulation is 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 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 and a Ph. Eur. Certificate of Suitability has been supplied. Milbemycin oxime is not described in a pharmacopeia 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 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 and yeast powder, are described in the European Pharmacopoeia and are manufactured in accordance with the relevant Ph. Eur. Monograph. Data were provided for the manufacture of meat flavour and yeast powder. 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 6 months after halving the 2.5 mg/125 mg 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

The shelf life of the finished product as packaged for sale is 3 years.
Store in the original packaging in order to protect from moisture. This veterinary medicinal product does not require any special temperature storage conditions.

Applicable to Milbactor 2.5 mg/ 25 mg Tablets only:
Shelf life of halved tablets after first opening the immediate packaging is 6 months.
Halved tablets should be stored below 25°C in the original blister and be used for the next administration.
Keep the blister in the outer carton.

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.
- Part tablets should be returned to the open blister pocket and inserted into the outer carton.

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

Bioequivalence Study

An *in vivo* bioequivalence study was provided comparing the 12.5 mg/ 125 mg tablet with the reference product. The study had a single dose, crossover design. The test product and reference product was administered to 24 healthy, male dogs with a 30 day washout period between treatments. Animals were fasted overnight before treatment.

Blood samples were taken on the day before treatment and at regular intervals after treatment until 480 hours post treatment. The concentration of milbemycin oxime and praziquantel was established. The AUC[3], C_{max}[4] and T_{max}[5] were determined for both milbemycin oxime and praziquantel. Both ANOVA and 90% confidence intervals for the pivotal parameters, AUC and C_{max}, were used to determine bioequivalence.

The results for the test product for milbemycin oxime were AUC = 19670.5 (±6614.19) h*ng/mL, C_{max} = 744.78 (±252.52) ng/mL and T_{max} = 1.79 (±0.84) h. The results for the reference product for milbemycin oxime were AUC = 20095.89 (±6781.93) h*ng/mL, C_{max} = 716.47(±285.53) ng/mL and T_{max} = 1.55 (±0.69) h.

The results for praziquantel following administration of the test product were AUC = 2178.41 (±660.34) h*ng/mL, C_{max} = 1559.40 (±653.42) ng/mL and T_{max} = 0.96 (±0.58) h. The results for the reference product for praziquantel were AUC = 2167.44 (±776.11) h*ng/mL, C_{max} = 1495.48 (±711.83) ng/mL and T_{max} = 0.77 (±0.34) h.

The 90% confidence intervals for the pivotal parameters for both milbemycin oxime and praziquantel fell within the predefined acceptance limits (80 – 125%).

[3] AUC – Area Under the Curve
[4] C_{max} – Maximum plasma concentration
[5] T_{max} – Time to maximum concentration

Therefore bioequivalence is accepted between the test product and the reference product.

Dissolution Study

A dissolution study was provided for the 2.5 mg/ 25 mg tablet for comparison with the 12.5 mg/125 mg test and reference products. The dissolution profiles of the tablets were compared using 3 dissolution media at different pH; 1.0, 4.5 and 7.4. The dissolution profiles were then compared for the three 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 all 3 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. In addition, the applicant conducted an in vivo bioequivalence study and the test product was well tolerated by the dogs 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

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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.

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

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.

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