Veterinary Medicines Directorate

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

## NATIONAL PROCEDURE

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

**Ezi-Wormer Duo 12.5/125 mg Flavoured Tablets for Dogs (Milbemycin/Praziquantel)**
**Ezi-Wormer Duo 2.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies (Milbemycin/Praziquantel)**
**Milbemycin/Praziquantel (EU Generics) 12.5 mg/125 mg Flavoured Tablets for Dogs**
**Milbemycin/Praziquantel (EU Generics) 2.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies**
**Milbemycin/Praziquantel 12.5 mg/125 mg Flavoured Tablets for Dogs**
**Milbemycin/Praziquantel 2.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies**
**Milpradog 12.5/125 mg Flavoured Tablets for Dogs**
**Milpradog 2.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies**
**Quantilex 12.5/125 mg Flavoured Tablets for Dogs (Milbemycin/Praziquantel)**
**Quantilex.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies (Milbemycin/Praziquantel)**
**Ridaworm Duo 12.5/125 mg Flavoured Tablets for Dogs (Milbemycin/Praziquantel)**
**Ridaworm Duo 2.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies (Milbemycin/Praziquantel)**
**Wormax Plus 12.5/125 mg Flavoured Tablets for Dogs (Milbemycin/Praziquantel)**
**Wormax 2.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies (Milbemycin/Praziquantel)**
**Wormit Plus12.5/125 mg Flavoured Tablets for Dogs (Milbemycin/Praziquantel)**
**Wormit Plus2.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies (Milbemycin/Praziquantel)**

**Date Created: March 2020**

# MODULE 1

## PRODUCT SUMMARY

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| Name, strength and pharmaceutical form | Ezi-Wormer Duo 12.5/125 mg Flavoured Tablets for Dogs (Milbemycin/Praziquantel)<br>Ezi-Wormer Duo 2.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies (Milbemycin/Praziquantel)<br>Milbemycin/Praziquantel (EU Generics) 12.5 mg/125 mg Flavoured Tablets for Dogs<br>Milbemycin/Praziquantel (EU Generics) 2.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies<br>Milbemycin/Praziquantel 12.5 mg/125 mg Flavoured Tablets for Dogs<br>Milbemycin/Praziquantel 2.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies<br>Milpradog 12.5/125 mg Flavoured Tablets for Dogs<br>Milpradog 2.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies<br>Quantilex 12.5/125 mg Flavoured Tablets for Dogs (Milbemycin/Praziquantel)<br>Quantilex.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies (Milbemycin/Praziquantel)<br>Ridaworm Duo 12.5/125 mg Flavoured Tablets for Dogs (Milbemycin/Praziquantel)<br>Ridaworm Duo 2.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies (Milbemycin/Praziquantel)<br>Wormax Plus 12.5/125 mg Flavoured Tablets for Dogs (Milbemycin/Praziquantel)<br>Wormax 2.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies (Milbemycin/Praziquantel)<br>Wormit Plus12.5/125 mg Flavoured Tablets for Dogs (Milbemycin/Praziquantel)<br>Wormit Plus2.5 mg/25 mg Flavoured Tablets for Small Dogs and Puppies (Milbemycin/Praziquantel) |
| Applicant | EU Generics Limited<br>37 Geraldine Road, London, SW18 2NR |
| Active substance | Milbemycin<br>Praziquantel |
| ATC Vetcode | QP54A B51 (Milbemycin combinations) |
| Target species | Dogs |
| Indication for use | In dogs: treatment of mixed infections by adult cestodes and nematodes of the following species:<br><br>- Cestodes:<br>*Dipylidium caninum*<br>*Taenia spp.*<br>*Echinococcus spp.* |

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| | *Mesocestoides spp.*<br><br>- Nematodes:<br>*Ancylostoma caninum*<br>*Toxocara canis*<br>*Toxascaris leonina*<br>*Trichuris vulpis*<br>*Crenosoma vulpis* (Reduction of the level of infection)<br>*Angiostrongylus vasorum* (Reduction of the level of infection by immature adult (L5) and adult parasite stages; see specific treatment and disease prevention schedules under SPC point “4.9 Amounts to be administered and administration route”)<br>*Thelazia callipaeda* (see specific treatment schedule under section 4.9 “Amounts to be administered and administration route”)<br><br>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 Product Information Database of the Veterinary Medicines Directorate.

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

# MODULE 3

## PUBLIC ASSESSMENT REPORT

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|---|---|
| Legal basis of original application | Generic applications in accordance with Article 13 (1) of Directive 2001/82/EC as amended. |
| Date of conclusion of the procedure | 29th January 2020 |

## I. SCIENTIFIC OVERVIEW

These were applications for generic products as cited above, the products are indicated for use in dogs and puppies, as detailed in the Summaries of Product Characteristics, (SPCs). The reference product for the higher strength proposed products is Milbemax Tablets for Dogs, authorised in the UK since April 2003. An *in vivo* bioequivalence study was carried for these products. For the lower strength products, the applicant claimed exemption from the requirement for bioequivalence studies and submitted comparative dissolution studies.

The product is 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 product 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[1] 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.

## II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

### *II.A. Composition*

The products contain milbemycin and praziquantel and the excipients cellulose, microcrystalline, croscarmellose sodium, povidone, lactose monohydrate, silica, colloidal anhydrous, magnesium stearate, talc, artificial powdered beef flavour and yeast extract.

The container/closure system consists of blisters consisting of clear PVC/PE/PVDC film and an aluminium foil.
Boxes contain 2, 4, 8, 10, 20, 30, 50, 100, 200 or 500 tablets in blisters.
The particulars of the containers and controls performed are provided and conform to the regulation.

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

The choice of the formulation and the absence of preservative are justified.

The products are in an established pharmaceutical form and development is adequately described in accordance with the relevant European guidelines.

### *II.B. Description of the Manufacturing Method*

The products are manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a granulation process, followed by compression of the mixture into tablets

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 and praziquantel, established active substances described in the European Pharmacopoeia (Ph. Eur). The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Acceptable Certificates of Suitability were provided. Suitable documentation was provided, detailing the appropriateness of the excipients and packaging used.

### *II.C.4. Substances of Biological Origin*

Scientific data and certificates of suitability 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. The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

### *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 sites have been

provided demonstrating compliance with the specification. Control tests on the finished product include those for:

### *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.

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.

### *G. Other Information*

12.5 mg/125 mg products
Shelf-life of the veterinary medicinal product as packaged for sale: 18 months
Do not store above 25°C.
Keep blister in the outer carton to protect from light.

2.5mg /25 mg products
Shelf-life of the veterinary medicinal product as packaged for sale: 18 months
Any unused half tablets should be returned to the open blister and discarded after 4 weeks.
Do not store above 25°C.
Keep blister in the outer carton to protect from light.

## II. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

Due to the nature of the application, no toxicological or pharmacological data, other than that to support bioequivalence were required.

### *III.A Safety Documentation*

### *Pharmacological Studies*

Pharmacodynamics

Milbemycin oxime belongs to the group of macrocyclic lactones, isolated from the fermentation of *Streptomyces hygroscopicus* var. *aureolacrimosus*. It is active against mites, against larval and adult stages of nematodes as well as against larvae of *Dirofilaria immitis*.

The activity of milbemycin is related to its action on invertebrate neurotransmission: Milbemycin oxime, like avermectins and other milbemycins, increases nematode and insect membrane permeability to chloride ions via glutamate-gated chloride ion channels (related to vertebrate $GABA_A$ and glycine

receptors). This leads to hyperpolarisation of the neuromuscular membrane and flaccid paralysis and death of the parasite.

Praziquantel is an acylated pyrazino-isoquinoline derivative. Praziquantel is active against cestodes and trematodes. It modifies the permeability for calcium (influx of Ca2+) in the membranes of the parasite inducing an imbalance in the membrane structures, leading to membrane depolarisation and almost instantaneous contraction of the musculature (tetany), rapid vacuolization of the syncytial tegument and subsequent tegumental disintegration (blebbing), resulting in easier expulsion from the gastrointestinal tract or death of the parasite

Pharmacokinetics

After oral administration of praziquantel in the dog, peak serum levels of parent are rapidly attained ($T_{max}$ approximately 0.5-4 hours) and decline quickly ($t_{1/2}$ approximately 1.5 hours); there is a substantial hepatic first-pass effect, with very rapid and almost complete hepatic biotransformation, principally to monohydroxylated (also some di- and tri-hydroxylated) derivatives, which are mostly glucuronide and/or sulfate conjugated before excretion. Plasma binding is about 80%. Excretion is fast and complete (about 90% in 2 days); the principal route of elimination is renal.

After oral administration of milbemycin oxime in dogs, peak plasma levels occur at about 2-4 hours, and decline with a half-life of the unmetabolised milbemycin oxime of 1-4 days. Bioavailability is about 80%. In the rat, metabolism appears to be complete although slow, since unchanged milbemycin oxime has not been found in urine or faeces. Main metabolites in the rat are monohydroxylated derivatives, attributable to hepatic biotransformation. In addition to relatively high liver concentrations, there is some concentration in fat, reflecting its lipophilicity.

## *User Safety*

A user risk assessment was provided in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following applicant's user recommendations are appropriate:

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.

Other precautions

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*

The applicant has performed and submitted a Phase I ERA in accordance with VICH guidelines. Assessment ends at Phase I based on use in non-food producing animals only. The disposal advice given in the SPCs and product literature is acceptable and the products are not expected to pose a risk to the environment when used as recommended.

## IV. CLINICAL DOCUMENTATION

A bioequivalence study comparing the higher strength proposed product to the reference product, and dissolution studies to then infer bioequivalence with the higher strength products were carried out.

The in vivo bioequivalence study was a GLP[2], two-period, two sequence, crossover study in 24 dogs, conducted to establish bioequivalence between the reference product and the proposed, higher strength product. The washout period was 28 days. Animals were divided equally into two groups, and each animal received a single dose of either the proposed or the reference product.

Blood samples were taken at appropriate time points, and suitable statistical processes were used to determine bioequivalence using key pharmacokinetic parameters ($AUC^{0-t}$ and $C_{max}$). Results showed that the 90% confidence intervals for the ratios o the test:reference products was within the limits of 80% - 125%. Bioequivalence was therefore established.

Suitable dissolution studies permitted that the qualities of the higher strength tablet could satisfactorily be extrapolated to the lower strength product, confirming the required efficacy by this means.

### *IV.I. Pre-Clinical Studies*

As bioequivalence was confirmed by appropriate bioequivalence and dissolution studies, no further data were required in this section.

### *Tolerance in the Target Species*

As bioequivalence was confirmed by appropriate bioequivalence and dissolution studies, no further data were required in this section.

### *IV.II. Clinical Documentation*

### *Laboratory Trials*

As bioequivalence was confirmed by appropriate bioequivalence and dissolution studies, no further data were required in this section.

[2] GLP – Good Laboratory Practice.

# V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the products are used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the products 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.

(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)