



**Veterinary
Medicines
Directorate**

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

NATIONAL PROCEDURE

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY
MEDICINAL PRODUCT**

**Milbemycin Oxime Praziquantel Alfamed II 12.5 mg / 125.0 mg Chewable
Tablets for Dogs**

**Milbemycin Oxime Praziquantel Alfamed II 2.5 mg / 25.0 mg Chewable
Tablets for Small Dogs and Puppies**

**Milbemycin Oxime Praziquantel Alfamed II 25.0 mg / 250.0 mg Chewable
Tablets for Large Dogs**

Date Created: February 2025

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Milbemycin Oxime Praziquantel Alfamed II 2.5 mg / 25.0 mg Chewable Tablets for Small Dogs and Puppies Milbemycin Oxime Praziquantel Alfamed II 12.5 mg / 125.0 mg Chewable Tablets for Dogs Milbemycin Oxime Praziquantel Alfamed II 25.0 mg / 250.0 mg Chewable Tablets for Large Dogs
Applicant	Alfamed, 13ème rue - L.I.D, Carros Cedex, 06517, France
Active substance	Milbemycin Oxime (A3 and A4) Praziquantel
ATC Vetcode	QP54AB51
Target species	Dogs
Indication for use	<p>In dogs: treatment of mixed infections by adult cestodes and nematodes of the following species:</p> <p>- Cestodes: <i>Dipylidium caninum</i> <i>Taenia spp.</i> <i>Echinococcus spp.</i> <i>Mesocestoides spp.</i></p> <p>- Nematodes: <i>Ancylostoma caninum</i> <i>Toxocara canis</i> <i>Toxascaris leonina</i> <i>Trichuris vulpis</i> <i>Crenosoma vulpis</i> <i>Angiostrongylus vasorum</i> <i>Thelazia callipaeda</i></p> <p>The product can also be used in the prevention of heartworm disease (<i>Dirofilaria immitis</i>) if concomitant treatment against cestodes is indicated.</p>

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 8 of VMRs 2013 (Schedule 1, Para 10) as amended. Generic hybrid application in accordance with Article 8 of VMRs 2013 (Schedule 1, Para 10a) as amended.
Date of conclusion of the procedure	8/11/2024

I. SCIENTIFIC OVERVIEW

Milbemycin Oxime Praziquantel Alfamed II 2.5 mg / 25.0 mg Chewable Tablets for Small Dogs and Puppies and Milbemycin Oxime Praziquantel Alfamed II 12.5 mg / 125.0 mg Chewable Tablets for Dogs are generic applications with the reference products being Milbemax Chewable Tablets (for Small Dogs and Puppies or for Dogs respectively) which have been authorised in the UK since 2010.

Milbemycin Oxime Praziquantel Alfamed II 25.0 mg / 250.0 mg Chewable Tablets for Large Dogs is a generic hybrid application with the reference product being Milbemax Chewable Tablets for Dogs. It is considered a hybrid application as the tablet strength differs from that of the reference product.

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.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 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 and the excipients: meat flavour, maize starch, glycerol, croscarmellose sodium, microcrystalline cellulose, macrogol 3350 (E1520), confectioner's sugar, soya-bean oil, purified water, sodium chloride, ferric oxide (E172) and butylhydroxyanisole (E320).

The container/closure system consists of a coated OPA/aluminium/PVC foil blister pack. 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 regulatory 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.

Process validation data on the product have been presented in accordance with the relevant regulatory guidelines.

II.C. Control of Starting Materials

The active substances are milbemycin oxime and praziquantel which are established active substances described in the European Pharmacopoeia. 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 comply with Ph. Eur. or USP except for meat flavour which CoAs are provided.

II.C.4. Substances of Biological Origin

Scientific data and/or 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. 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 are those appropriate for this pharmaceutical form.

II.F. Stability

Stability data on the active substances have been provided in accordance with applicable regulatory 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

Shelf life of the veterinary medicinal product as packaged for sale: 21 months.

Do not store above 25°C.

Store in the original package to protect from light.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACOTOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Bibliographical data has been provided which show that 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 Ca^{2+}) 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.

After oral administration of praziquantel in the dog, peak serum levels of parent are rapidly attained (T_{max} approximately 0.5-12 hours) and decline quickly ($t_{1/2}$ approximately 1.85 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 2-6 hours, and decline with a half-life of the unmetabolised milbemycin oxime of 2.5 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.

Toxicological Studies

Not required due to the legal basis of the application.

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:

This veterinary medicinal product may cause hypersensitivity reactions. People with known hypersensitivity to butylhydroxyanisole, macrogols or soya (bean) oil should avoid contact with the veterinary medicinal product. If contact occurs, wash hands and seek medical advice in case of hypersensitivity reactions.

This veterinary medicinal product may be harmful after accidental ingestion. To avoid accidental ingestion, particularly by a child, blister cards should be inserted back into the carton and kept out of sight and reach of children. In case of accidental ingestion of the tablets, seek medical advice immediately and show the package leaflet or the label to the physician.

Wash hands after use.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

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

Not required due to the legal basis of the application. Bioequivalence was established with regards to the reference product.

IV.II. Clinical Documentation

Not required due to the legal basis of the application.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that the benefit/risk profile of the products are 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.

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