Milbemycin oxime / Praziquantel Alfamed II	National
Applicant	ALFAMED
Publicly available assessment report	

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AGENCE NATIONALE DU
MEDICAMENT VETERINAIRE

FRENCH AGENCY FOR FOOD, ENVIRONNEMENTAL AND OCCUPATIONAL HEALTH SAFETY

FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS

14 RUE CLAUDE BOURGELAT – PARC D'ACTIVITES DE LA GRANDE MARCHE JAVENE – CS 70611 – 35306 FOUGERES

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

MILBEMYCINE OXIME PRAZIQUANTEL ALFAMED II 2,5 MG/25 MG COMPRIMES PELLICULES POUR PETITS CHIENS ET CHIOTS

MILBEMYCINE OXIME PRAZIQUANTEL ALFAMED II 12,5 MG/125 MG COMPRIMES PELLICULES POUR CHIENS

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PRODUCT SUMMARY

Name, strength and pharmaceutical form	Milbemycin oxime Praziquantel Alfamed II 2.5 mg/25 mg film-coated tablets for small dogs and puppies Milbemycin oxime Praziquantel Alfamed II 12.5 mg/125 mg film-coated tablets for dogs
Applicant	ALFAMED 13eme Rue 06510 Carros FRANCE
Active substance(s)	praziquantel milbemycin oxime
ATC vetcode	QP54AB51
Target species	Dogs (weighing more than 0.5 kg) Dogs (weighing more than 5 kg)
Indication for use	For dogs with, or at risk from mixed infections of cestodes, nematodes and/or heartworm. The veterinary medicinal product is only indicated when the use to treat or prevent all the following infections is required at the same time. Cestodes Treatment of tapeworms: Dipylidium caninum, Taenia spp., Echinococcus spp., Mesocestoides spp. Gastrointestinal nematodes Treatment of: Hookworm: Ancylostoma caninum Roundworms: Toxocara canis, Toxascaris leonina Whipworm: Trichuris vulpis Eyeworm Treatment of Thelazia callipaeda (see specific treatment schedule under section 3.9 “Administration routes and dosage”).

	Lungworms Treatment of: Angiostrongylus vasorum (Reduction of the level of infection by immature adult (L5) and adult parasite stages; see specific treatment and prevention disease schedules under section 3.9 “Amount(s) to be administered and administration route”), Crenosoma vulpis (Reduction of the level of infection). Heartworm Prevention of heartworm disease (Dirofilaria immitis) if concomitant treatment against cestodes is indicated.

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PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

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SUMMARY OF ASSESSMENT

Legal basis of original application*	Hybrid application in accordance with Article 19 of Regulation (EC) 2019/6 as amended.
Reference product (RP)	MILBEMAX COMPRIMES POUR PETITS CHIENS ET CHIOTS
Marketing authorisation holder	Elanco GmbH
Marketing authorisation number	FR/V/6738555 1/2002
Date of authorisation	01/2002

Legal basis of original application*	Hybrid application in accordance with Article 19 of Regulation (EC) 2019/6 as amended.
Reference product (RP)	MILBEMAX COMPRIMES POUR CHIENS
Marketing authorisation holder	Elanco GmbH
Marketing authorisation number	FR/V/7374799 2/2002
Date of authorisation	02/2002

1. SCIENTIFIC OVERVIEW

The veterinary medicinal products (VMP) are produced and controlled using validated methods and tests, which ensure the consistency of the VMPs released on the market.

It has been shown that the VMPs can be safely used in the target species; the reactions observed are indicated in the SPC.

The VMPs are safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.

The efficacy of the VMPs was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

A. Product description

The VMPs contain the active substances praziquantel and milbemycin oxime (2.5 mg/25 mg for puppy and small dogs film-coated tablets and 12.5 mg/125 mg for dogs film-coated tablets). The excipients are the following ones: cellulose microcrystalline, croscarmellose sodium, lactose monohydrate, povidone (K30), starch pregelatinised, magnesium stearate, silica hydrophobic colloidal, poultry liver powder, hypromellose and macrogol stearate.

The container closure system is oriented Polyamide/Aluminium/Polyvinyl Chloride blister with an aluminium thermo-sealable lidding foil.

The choice of the formulation is justified.

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

B. Description of the manufacturing method

The VMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

Process validation data on the VMP have been presented in accordance with the relevant European guidelines.

C. Production and control of starting materials

The active substances are praziquantel and milbemycin oxime, established active substances. Both substances are described in the European Pharmacopeia. 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.

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.

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this VMP.

Starting materials of non-biological origin used in production comply with indicate pharmacopoeia monographs.

Biological starting material used is in compliance with the relevant Ph. Eur. Monographs and guidelines and is appropriately assessed for the absence of extraneous agents according to the Ph. Eur.

D. Control tests carried out on isolated intermediates during the manufacturing process

Not applicable.

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 VMP.

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.

F. Stability tests

A re-test period is mentioned on the certificates of suitability covering both active substances.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the VMP throughout its shelf life when stored under the approved conditions.

G. Other information

Not applicable.

3. SAFETY DOCUMENTATION (safety and residues tests)

As these are hybrid application according to Article 19 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has not been demonstrated, safety data provided from the literature.

The toxicological aspects of these VMP are identical to the reference VMP.

Warnings and precautions as listed on the product literature are the same as those of the reference VMPs and are adequate to ensure safety of the product to users / the environment.

A. Safety tests

Pharmacological studies

The applicant provided bibliographical data describing the pharmacodynamic and toxicological properties of both active substances.

User safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the VMP.

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the VMP will only be used in non-food animals.

No warning is necessary.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

As these are hybrid application according to Article 19 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has not been demonstrated, data to support efficacy have been provided and evaluated.

The efficacy claims for these VMPs are the same as for the reference products.

A. Pre-Clinical Studies

Pharmacology

The applicant has submitted pharmacokinetic studies, bioequivalence studies and dissolution studies to support the bioequivalence with the reference VMP. Based on these data, the bioequivalence was not demonstrated.

Development of resistance and related risk in animals

The bibliography reported resistance of *Dipylidium caninum* to praziquantel*, of Ancylostoma caninum to milbemycine oxime and resistance of Dirofilaria immitis to macrocyclic lactones*.

Adequate warnings and precautions appear on the product literature.

Dose determination and confirmation

No dose determination was conducted with the VMP but provided literature confirmed minimum recommended dose rates of 0.5 mg/kg for milbemycin oxime and 5.0 mg/kg for praziquantel.
In support of the efficacy of the VMP, the applicant has provided has provided well conducted dose confirmation studies and relevant bibliographical references. These studies and publications allow to justify efficacy against *Dipylidium caninum*, *Taenia* spp., *Echinococcus* spp.,*Mesocestoides* spp., *Ancylostoma caninum*, *Toxocara canis*, *Toxascaris leonina*, *Trichuris vulpis*, *Thelazia callipaedia*, *Crenosoma vulpis* and *Angiostrongylus vasorum* and the efficacy for the use for the prevention against *Dirofilaria immitis.*

Tolerance in the target species of animals

No tolerance studies have been conducted with the VMP.

The tolerance profile is similar to the reference VMP.

The product literature accurately reflects the type and incidence of adverse effects, which might be expected.

B. Clinical trials

Please see *dose determination and confirmation*

No clinical trials were performed.

The absence of clinical trials was justified based on the hybrid application according to Article 19 of Regulation (EC) 2019/6) and on results of dose confirmation studies.

Claimed indications are the same as those of the reference products.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMPs are used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the VMPs for humans and the environment is acceptable.