IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Milbepar 12.5 mg / 125 mg chewable tablets for dogs

PRODUCT SUMMARY

EU Procedure number	IE/V/0887/002/DC
Name, strength and pharmaceutical form	Milbepar 12.5 mg / 125 mg chewable tablets for dogs
Active substances(s)	Milbemycin oxime,Praziquantel
Applicant	Ceva Santé Animale 10, avenue de La Ballastière 33500 Libourne France
Legal basis of application	Generic application (Article 18 of Regulation (EU) 2019/6)
Date of completion of procedure	07/05/2024
Target species	Dogs weighing at least 2.5 kg
Indication for use	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 prevention disease schedules under SPC section 3.9 'Administration routes and dosage'). *Thelazia callipaeda* (see specific treatment schedule under SPC section 3.9 'Administration routes and dosage). The product can also be used in the prevention of heartworm disease (*Dirofilaria immitis*) if concomitant treatment against cestodes is indicated.
ATCvet code	QP54AB51
Concerned Member States	FR

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in the relevant Articles of Regulation (EU) 2019/6. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland. The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

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; the 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 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. QUALITY ASPECTS

II.A. Composition
The product contains milbemycin oxime (12.5 mg/tablet) and praziquantel (125 mg/tablet) as active substances. The excipients are croscarmellose sodium, povidone, lactose monohydrate, cellulose microcrystalline, silica colloidal anhydrous, magnesium stearate, chicken flavour and yeast.
The container/closure system consists of blister packs.
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 at a licensed manufacturing site. Process validation data for the manufacturing process has 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 described in the European Pharmacopoeia. 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 materials. Batch analytical data demonstrating compliance with the specifications have been provided.

II.C.4. Substances of Biological Origin
Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies
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.

II.F. Stability
Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances 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
Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 18, and bioequivalence with a suitable reference product has been demonstrated, results of safety tests are not required. The reference product cited by the applicant is Milbemax tablets for dogs (RMS VPA: 22020/008/002, MAH Elanco GmbH).
The safety aspects of this product are considered to be the same as the reference product.
Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and the environment.

III. SAFETY ASSESSMENT

Pharmacological Studies

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

The applicant conducted a pivotal *in vivo* bioequivalence study in which equivalence of the 12.5 mg / 125 mg tablet strength of the candidate product, and the same tablet strength of the reference product (Milbemax tablets for dogs) was investigated in 40 Beagle dogs. The study was conducted to GLP-standard and in accordance with relevant guidance. 1 tablet of the candidate / reference product was administered to dogs with a 28-day wash-out period. The evaluation of bioequivalence was based upon validated measurement of the active substances milbemycin A3 and milbemycin A4 (sum of A3 and A4), and praziquantel, in plasma. Based on the results of this study, equivalence in respect of AUC for milbemycin and praziquantel, and C_{max} for milbemycin was demonstrated (90% confidence intervals for the ratio of the means were between 80 and 125%). While the upper 90% confidence intervals for the ratio of the means for C_{max} for praziquantel was greater than 125%, widened acceptance criteria were pre-specified in the study protocol, and it was accepted based on justification provided by the applicant and target animal tolerance study data that this result was not expected to have a clinically significant impact on the safety or efficacy profile of the candidate product. As such, bioequivalence between the 12.5 mg / 125 mg tablet strengths of the candidate and reference products was accepted.

In vitro dissolution data were provided and considered sufficient to permit extrapolation of the results of the *in vivo* bioequivalence study (using the 12.5 mg / 125 mg tablet strength) to the 2.5 mg / 25 mg and the 25 mg / 250 mg tablet strengths of the candidate product.

Toxicological Studies

The applicant provided bibliographic data concerning the toxicology of the active substances milbemycin oxime and praziquantel. The omission of proprietary toxicological data was accepted based on the demonstration of bioequivalence between the candidate and reference products.

Other Studies

The applicant provided special (local effect) studies that investigated the potential of the candidate formulation for skin/ocular irritation and skin sensitisation. Based on the studies provided it was concluded that the 25 mg / 250 mg tablet strength of the candidate product is not a skin, or an ocular irritant, but has weak skin sensitisation potential.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. The applicant has proposed user safety warnings that are similar to those included in the SPC of the reference product, and also take into account the potential for skin sensitisation.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product, as follows:

This veterinary medicinal product may be harmful when ingested, particularly for children. To avoid accidental ingestion, the product should be stored out of sight and reach of children. Any unused tablet parts should be returned to the opened blister, inserted back into the outer packaging and used at the next administration or securely discarded (see section 5.5).

In case of accidental ingestion of the tablets, particularly by a child, seek medical advice immediately and show the package leaflet or the label to the physician.

The product may cause a weak skin sensitisation. Do not handle this product in case of known hypersensitivity to the active substances or to any of the excipients.

If symptoms such as skin rash persist, seek medical advice and show the package leaflet or the label to the physician. Wash hands after use.

Environmental Risk Assessment

Phase I

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the candidate product will only be used in non-food producing species (i.e., dogs).

Conclusion

Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant conducted a GLP-compliant target animal tolerance study investigating dose rates of 1X and 3X times the highest recommended treatment dose of the candidate product in healthy puppies on 3 occasions, 2 weeks apart. The clinical observations reported (in the 3X group only) were all self-limiting, had resolved by the day following administration and were consistent with the adverse events described in the SPC of the reference product. At 1X the highest recommended dose, no adverse reactions were observed.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance
The bibliographic information provided with this application indicates that there is recent clinical evidence of emerging resistance of *Dipylidium caninum* to praziquantel. Resistance of *Dirofilaria immitis* to milbemycin has been confirmed, and there is evidence of emerging anthelmintic (including milbemycin) resistance in *Ancyclostoma caninum*. All reports cited originate from the USA.
Adequate warnings and precautions concerning resistance appear on the product literature.

IV.B Clinical Studies
As this is a generic application according to Article 18, and bioequivalence with a reference product has been demonstrated, the results of efficacy studies are not required. The efficacy profile of the candidate product is accepted as being the same as that of the reference product.
The applicant conducted a GCP-compliant study to investigate the palatability of the candidate product in dogs, however the results of this study were insufficient to support a palatability claim in the product information.

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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.