IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Milbetrin 12.5 mg/125 mg Tablets for Dogs

PRODUCT SUMMARY

EU Procedure number	IE/V/0409/001/DC
Name, strength and pharmaceutical form	Milbetrin 12.5 mg/125 mg Tablets for Dogs
Active substance(s)	Milbemycin oxime, Praziquantel
Applicant	Chanelle Pharmaceuticals Manufacturing Limited Loughrea Co. Galway Ireland
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of procedure	06/02/2019
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 SPC point 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.
ATCvet code	QP54AB51
Concerned Member States	DE, IT, NL

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the 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 Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. 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 adverse reactions that may be 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 by way of reference to a reference product.
The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

II.A. Composition
The product contains milbemycin oxime and praziquantel as active substances. The excipients are cellulose (microcrystalline), lactose monohydrate, povidone K30, croscarmellose sodium, colloidal anhydrous silica, meat flavour, yeast extract. talc and magnesium stearate.
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 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. Milbemycin oxime is not described in a 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 materials. Batch analytical data demonstrating compliance with the specifications have been provided.
All of the excipients, apart from meat flavour and yeast powder, are described in the European Pharmacopoeia. Data were provided for the manufacture of meat flavour and yeast powder.

II.C.4. Substances of Biological Origin
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.
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)

This application has been submitted in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC (a generic veterinary medicinal product). The candidate formulation represents a fixed combination of milbemycin oxime and praziquantel containing 12.5 mg milbemycin oxime & 125 mg praziquantel.
The reference veterinary medicinal product cited by the Applicant is Milbemax tablets for dogs (VPA 10397/020/002 – Elanco Europe Ltd) which was first granted a marketing authorisation in the RMS on 08/08/2003 following a Mutual Recognition procedure.
Warnings and precautions as listed on the product literature are consistent with those of the reference product and other similar products recently authorised within the EU and are considered adequate to ensure safety of the product for the animal, users and the environment.

III.A Safety Testing

Pharmacological Studies

Results of a well-conducted GLP-compliant *in-vivo* bioequivalence study were provided comparing candidate and reference formulations. Plasma concentrations of milbemycin oxime A3, milbemycin oxime A4 and praziquantel were measured following a single administration. Milbemycin oxime is a mixture of two compounds (milbemycin oxime A3 and milbemycin oxime A4 in the ratio of about 1:4).
Results indicate that the 90% confidence interval of the ratio (Test/Reference) of least-squares means from the ANOVA of the ln-transformed AUC_t and C_{max} parameters falls within the limits of 80-125% for both AUC_t and C_{max} for all three active moieties (milbemycin oxime A3, milbemycin oxime A4 and praziquantel).
Based on the above results, it was accepted that the product has been demonstrated to be bioequivalent to the reference product.
An acceptable validation of the analytical method used to determine milbemycin oxime (A3 & A4 forms) and praziquantel concentrations in canine plasma has been provided.

Toxicological Studies

As bioequivalence with the reference product has been satisfactorily demonstrated, the omission of toxicological data was accepted.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.
Given that bioequivalence with the reference product was accepted and no additional risks for the user were identified, it was accepted that the product will not present an unacceptable risk for the user when stored, handled, administered and disposed of in accordance with the recommendations included in the proposed SPC.
Warnings and precautions as listed on the product literature are considered adequate to ensure safety to users of the product.

Environmental Risk Assessment

Phase I

The Applicant provided an environmental risk assessment as required by the legislation and has followed the Phase I decision tree to determine that as the product is only intended for use in non-food producing species, the assessment may stop in Phase I.

Conclusion

It can be concluded that the product will not present an unacceptable risk for the environment when stored, handled, administered and disposed of in accordance with the recommendations included in the proposed SPC.

III.B Residues Documentation

Not applicable.

IV. CLINICAL ASSESSMENT

As this is a generic application according to Article 13(1) of Directive 2001/82/EC and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Pharmacology

Results of a well-conducted GLP-compliant *in-vivo* bioequivalence study were provided comparing candidate and reference formulations. Plasma concentrations of milbemycin oxime A3, milbemycin oxime A4 and praziquantel were measured following a single administration. Milbemycin oxime is a mixture of two compounds (milbemycin oxime A3 and milbemycin oxime A4 in the ratio of about 1:4).
Results indicate that the 90% confidence interval of the ratio (Test/Reference) of least-squares means from the ANOVA of the ln-transformed AUC_t and C_{max} parameters falls within the limits of 80-125% for both AUC_t and C_{max} for all three active moieties (milbemycin oxime A3, milbemycin oxime A4 and praziquantel).
Based on the above results, it was accepted that the product has been demonstrated to be bioequivalent to the reference product.
An acceptable validation of the analytical method used to determine milbemycin oxime (A3 & A4 forms) and praziquantel concentrations in canine plasma has been provided.

Tolerance in the Target Species of Animals

The Applicant provided *in-vivo* bioequivalence study data to demonstrate bioequivalence with the reference product and no adverse events were reported following administration of the candidate formulation to the dogs included in that study.
Further, the product is to be administered orally to dogs at the same posology for the same indications as already approved for the reference product. Having reviewed any possible differences between candidate and reference formulations, it was accepted that no difference in terms of target animal tolerance between candidate and reference formulations is to be expected.
Consequently, the omission of target animal tolerance data was accepted.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

Given the legal basis of this application (Art 13(1)) and the fact that the product is intended to be administered to the same target species using the same posology, no difference in terms of potential for resistance development is expected between candidate and reference formulations.
Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials & Field Trials

As this is a generic application according to Article 13(1) of Directive 2001/82/EC and bioequivalence with a reference product has been demonstrated, results of clinical studies were 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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. 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 HPRA website.

This section 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.

Changes:
None.