IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Amcofen 12.5 mg/125 mg film-coated tablets for dogs weighing at least 5 kg

PRODUCT SUMMARY

EU Procedure number	IE/V/0524/004/DX/001
Name, strength and pharmaceutical form	Amcofen 12.5 mg/125 mg film-coated tablets for dogs weighing at least 5 kg
Active substances(s)	Milbemycin oxime, Praziquantel
Applicant	Krka, d.d., Novo mesto Šmarješka cesta 6 8501 Novo mesto Slovenia
Legal basis of application	Extension application in accordancdw ithe Generic application (Article 13(1) of Directive No 2001/82/EC) as amended.
Date of Authorisation	28 July 2021
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 *Thelazia callipaeda* 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	BE, BG, CZ, DE, EE, ES, FR, HR, HU, IT, LT, LV, NL, PL, PT, RO, SI, SK, UK (NI)

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 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 slight 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

A. Qualitative and Quantitative Particulars

The product contains 12.5 mg milbemycin oxime and 125.0 mg praziquantel and the excipients cellulose, microcrystalline, lactose monohydrate, povidone, croscarmellose sodium, silica, colloidal anhydrous, meat flavour, yeast powder, magnesium stearate, hypromellose, talc, propylene glycol and liver flavour.
The container/closure system is blister packs consisting of cold formed aluminium foil, which consists of aluminium layer coated with OPA (Oriented Polyamide) film on one side and PVC on the other side and an aluminium sealing foil.
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

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.

C. Control of Starting Materials

The active substances are milbemycin oxime and praziquantel, 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 has been provided.

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.

D. Control on Intermediate Products

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 product.
Satisfactory validation data for the analytical methods has been provided.
Batch analytical data from the proposed production sites has been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substancse when stored under the approved conditions.
Stability data on the finished product has 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)

III.A Safety Testing

Pharmacological Studies

As this is an extension application for the addition of a new pharmaceutical form (film-coated tablets) in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC as amended (application for a generic veterinary medicinal product) and bioequivalence with a reference product has been accepted, results of pharmacological tests are not required.

Toxicological Studies

As this is an extension application for the addition of a new pharmaceutical form (film-coated tablets) in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC as amended (application for a generic veterinary medicinal product), and bioequivalence with a reference product has been demonstrated, results of toxicological tests are not required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the most likely routes of exposure are dermal, ocular through accidental hand to eye transfer or oral, again by accidental transfer or ingestion. The risk to the user is considered to be the same as for the reference product. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- Accidental ingestion of a tablet by a child may be harmful. In order to prevent children from accessing the product, tablets should be administered and stored out of sight and reach of children.
- Part tablets should be returned to the open blister pocket and inserted into the outer carton.
- In the event of accidental ingestion of one or more tablets, seek medical advice immediately and show the package leaflet or the label to the doctor.
- Wash hands after use.
- 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 (e. g. experts or institutes of parasitology).

Environmental Risk Assessment

An environmental risk assessment (ERA) was provided in accordance with VICH and CVMP guidelines.

Phase I:

The ERA concluded that the product is not expected to pose a risk to the environment when used as recommended in the SPC. 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 ASSESSMENT

IV.A Pre-Clinical Studies

As this is an extension application for the addition of a new pharmaceutical form (film-coated tablets) of the product to improve palatability, in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC as amended (application for a generic veterinary medicinal product), 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.

Pharmacology

Pharmacodynamics

As this is an extension application for the addition of a new pharmaceutical form (film-coated tablets) of the product to improve palatability, in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC as amended (application for a generic veterinary medicinal product), and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required. The product is considered to have the same pharmacodynamics particulars as the reference product.

Pharmacokinetics

As this is a line extension application for the addition of a new pharmaceutical form (film-coated tablets, with the only difference being film-coating excipients) and bioequivalence was previously demonstrated with the authorised chewable tablets, a new *in-vivo* bioequivalence study was not provided. To further justify the omission of a new *in-vivo* bioequivalence study, the applicant conducted a dissolution study.

Dissolution Study

A dissolution study was provided demonstrating the comparative dissolution profiles of both strengths of the current authorised chewable tablets against the film-coated tablets. The dissolution profiles of the tablets were compared using three dissolution media at different pH; 1.0, 4.5 and 7.4. The dissolution profiles were then compared for the products, with samples taken at various times. The curves were considered to be similar if the f2 (similarity factor) value was ≥50. The f2 values were all between 50 and 100, indicating similarity of the dissolution profiles. It was accepted that the dissolution profiles between the film-coated and chewable tablets were sufficiently similar to allow for the extrapolation of *in-vivo* bioequivalence with the reference product.

Tolerance in the Target Species of Animals

As this is a line extension application for the addition of a film-coated tablet and bioequivalence with the reference product was previously demonstrated with the chewable tablet, with the only difference being film-coating excipients in the candidate products (film-coated tablets), it can be accepted that target animal tolerance will be the same as that of the reference products. The applicant provided a study in support of a palatability claim for the film-coated tablets and that no adverse events were observed in this study. Consequently, it was accepted that no difference in target animal tolerance is expected for the film-coated tablets.

Resistance

As this is an extension application for the addition of a new pharmaceutical form (film-coated tablets) in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC as amended (application for a generic veterinary medicinal product), and bioequivalence with a reference product has been accepted, resistance data are not required.
Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

To demonstrate the claim of palatability of for the film-coated tablets, in accordance with the guidelines, the applicant conducted a palatability study in which the product was voluntarily accepted by > 80% of dogs in the study and the claim of palatability was accepted.

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.