IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Aderexa 2.5 mg/25 mg chewable tablets for small dogs and puppies weighing at least 0.5 kg

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PRODUCT SUMMARY

EU Procedure Number	IE/V/0528/001/MR
Name, Strength, Pharmaceutical Form	Aderexa 2.5 mg/25 mg chewable tablets for small dogs and puppies weighing at least 0.5 kg
Active Substances(s)	Milbemycin oxime,Praziquantel
Applicant	KRKA, d.d., Novo mesto Šmarješka cesta 6, 8501 Novo mesto Slovenia
Legal Basis of Application	Generic application (Article 13(1) of Directive No 2001/82/EC)
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.
ATC Code	QP54AB51

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

Aderexa 12.5/125.0 mg chewable tablets for dogs weighing at least 5kg and Aderexa 2.5/25 mg chewable tablets for small dogs and puppies weighing at least 0.5 kg have been developed as a generic products of Milbemax Tablets for Dogs and Milbemax Tablets for Small Dogs and Puppies. The reference products have been authorised in Ireland since 2003. Bioequivalence has been demonstrated between Aderexa 12.5/125.0 mg chewable tablets for dogs weighing at least 5 kg and Milbemax Tablets for Dogs. A biowaiver has been accepted for the lower tablet strength.

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The products contain milbemycin oxime and praziquantel, which should be administered at a dose rate of 0.5 mg/kg and 5 mg/kg respectively. Aderexa is indicated for the treatment of mixed infestations of adult cestodes and nematodes, as well as the prevention of heartworm disease. The products are contraindicated in animals where there is a known hypersensitivity to the active substance or any of the excipients.
The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto 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. 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 and praziquantel as active substances. The excipients are cellulose (microcrystalline), lactose monohydrate, povidone, croscarmellose sodium, colloidal anhydrous silica, meat flavour, yeast powder and magnesium stearate.
The container/closure system consists of cold formed OPA/Al/PVC foil and aluminium foil blister packs containing either 2 or 4 chewable tablets, packaged in a cardboard carton. Cartons contain 2, 4 or 48 chewable tablets.
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. The product is manufactured by mixing the active substances with povidone and croscarmellose sodium before adding purified water to granulate. The remaining excipients are then mixed with the granulate and the mix is compressed into tablets, which are then packaged. 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 and a Ph. Eur. Certificate of Suitability has been supplied. Milbemycin oxime is described in the European Pharmacopoeia and a Ph. Eur. Certificate of Suitability has been supplied. The active substances are 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 of the excipients, apart from meat flavour and yeast powder, are described in the European Pharmacopoeia and are manufactured in accordance with the relevant Ph. Eur. Monograph. Data were provided for the manufacture of meat flavour and yeast powder. Certificates of analysis were provided for all excipients.

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.

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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, including in-use stabilty 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.

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III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies
As this is a generic application in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required.

Toxicological Studies
As this is a generic application in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC as amended, 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 Safety
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

As this is a generic application in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC as amended, 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.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics
As this is a generic application in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC as amended, 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 "This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

Bioequivalence Study
An *in vivo* bioequivalence study was provided comparing the 12.5 mg/125 mg tablet with the reference product. The study had a single dose, crossover design. The test product and reference product was administered to 24 healthy, male dogs with a 30 day washout period between treatments. Animals were fasted overnight before treatment.

Blood samples were taken on the day before treatment and at regular intervals after treatment until 480 hours post treatment. The concentration of milbemycin oxime and praziquantel was established. The AUC, C_{max} and T_{max} were determined for both milbemycin oxime and praziquantel. Both ANOVA and 90% confidence intervals for the pivotal parameters, AUC and C_{max}, were used to determine bioequivalence.

The results for the reference product for milbemycin oxime were AUC approx. 20095.89 h*ng/mL, C_{max} approx. 716.47 ng/mL and T_{max} approx. 1.55 h. For the test product, respective results were within acceptance limits.

The results for the reference product for praziquantel were AUC approx. 2167.44 (±776.11) h*ng/mL, C_{max} approx. 1495.48 (±711.83) ng/mL and T_{max} approx. 0.77 (±0.34) h. For the test product, respective results were within acceptance limits.

The 90% confidence intervals for the pivotal parameters for both milbemycin oxime and praziquantel fell within the predefined acceptance limits (80 – 125%). Therefore bioequivalence is accepted between the test product and the reference product.

Dissolution Study
A dissolution study was provided for the 2.5 mg/ 25 mg tablet for comparison with the 12.5 mg/125 mg test and reference products. The dissolution profiles of the tablets were compared using 3 dissolution media at different pH; 1.0, 4.5 and 7.4. The dissolution profiles were then compared for the three products, with samples taken at various times.

The curves were considered to be similar if the f2 (similarity factor) value was ≥50. The results showed similar profiles for both milbemycin oxime and praziquantel all 3 products. The f2 values were all between 50 and 100, indicating similarity of the dissolution profiles.

Tolerance in the Target Species
As this is a generic application in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, results of tolerance studies are not required. In addition, the applicant conducted an in vivo bioequivalence study and the test product was well tolerated by the dogs in the study.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance
As this is a generic application in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, resistance data are not required. Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory Trials
As this is a generic application in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, results of laboratory trials are 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.

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VI. POST-AUTHORISATION ASSESSMENTS

None

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