College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Milpro Chewy 2.5 mg / 25.0 mg chewable tablets for small dogs and puppies
Milpro Chewy 12.5 mg / 125.0 mg chewable tablets for dogs
Milpro Chewy 25.0 mg / 250.0 mg chewable tablets for large dog

PRODUCT SUMMARY

EU procedure number	NL/V/0412/001-003/DC
Name, strength and pharmaceutical form	Milpro Chewy 2.5 mg / 25.0 mg chewable tablets for small dogs and puppies Milpro Chewy 12.5 mg / 125.0 mg chewable tablets for dogs Milpro Chewy 25.0 mg / 250.0 mg chewable tablets for large dogs
Applicant	VIRBAC 1ère avenue 2065 m LID 06516 Carros France
Active substance(s)	Milbemycin oxime, Praziquantel
ATC vetcode	QP54AB51
Target species	Dogs
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* *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 “Administration routes and dosage”) *Thelazia callipaeda* (see specific treatment schedule under section 3.9 “Administration routes and dosage”) The veterinary medicinal product can also be used in the prevention of heartworm disease (*Dirofilaria immitis*) if concomitant treatment against cestodes is indicated.

Milpro Chewy	NL/V/0412/001-003/DC
Virbac	DCP
Publicly available assessment report	

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).

SUMMARY OF ASSESSMENT

Legal basis of original application*	- Milpro Chewy 2.5 mg / 25.0 mg chewable tablets and Milpro Chewy 12.5 mg / 125.0 mg chewable tablets: generic application in accordance with Article 18 of Regulation (EC) 2019/6 as amended. - Milpro Chewy 25.0 mg / 250.0 mg chewable tablets: hybrid application in accordance with Article 19 of Regulation (EC) 2019/6 as amended.
Reference product (RP), *for Milpro Chewy 2.5 mg / 25.0 mg* Marketing authorisation holder MS where the RP is or has been authorised Marketing authorisation number EU procedure number Date of authorisation	MILBEMAX kauwtabletten voor kleine honden en puppy's Elanco GmbH NL REG NL 105573 FR/V/0135/005 November 2009
Reference product (RP), *for Milpro Chewy 25.0 mg / 250.0 mg and Milpro Chewy 12.5 mg / 125.0 mg* Marketing authorisation holder MS where the RP is or has been authorised Marketing authorisation number EU procedure number Date of authorisation	MILBEMAX kauwtabletten voor honden Elanco GmbH NL REG NL 105574 FR/V/0135/006 September 2009
Date of completion of the original decentralised procedure	8 May 2024
Date veterinary medicinal product first authorised in the Reference Member State (MRP only)	-

Concerned Member States for original procedure	AT DE BE FR ES IE PT IT EL PL FI NO DK SE BG CZ EE HR HU LT LV RO SI SK UK(NI)
Concerned Member States for subsequent recognition procedure	
Withdrawn CMS during original decentralised procedure	-

*Please be aware that certain parts of the dossier may be varied and consequently be subject to protection of technical documentation – for these and other changes of referenceability to parts of the dossier, please see chapter POST-AUTHORISATION PROCEDURES

1. SCIENTIFIC OVERVIEW

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

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

The VMP 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 VMP 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 VMP contains Praziquantel (S: 2.5 mg; M: 12.5 mg; L: 25 mg) and Milbemycin oxime (S: 25 mg; M: 125 mg; L: 250 mg) as active substances, and the excipients Meat flavour, Maize starch, Glycerol, Croscarmellose sodium, Microcrystalline cellulose, Macrogol 3350, Confectioner's sugar, Soya-bean oil, refined, Purified water, sodium chloride, Ferric oxide, and Butylhydroxyanisole. Traces of an antioxidant can be found in the excipient Macrogol.

The container/closure system is an Aluminium/Aluminium blister in a cardboard box.

The VMP is an established pharmaceutical form. Its development is adequately described.

The proposed QC dissolution method is acceptable, and its discriminatory power has been demonstrated.

A bioequivalence study has been conducted with one batch of the Medium strength of the test product vs one batch of the Medium strength of the reference product. For the Small and Large strengths, a biowaiver of strength has been requested. The dissolution conditions used for the biowaiver of strength are acceptable. The biowaiver of strength has been adequately demonstrated for the Small and the Large strengths at 3 different pH's. The comparative dissolution profile testing has been undertaken on three production batches per strength.

B. Description of the manufacturing method

The VMP is manufactured fully in accordance with the principles of good manufacturing practice. The manufacturing process and IPC's have been adequately described.

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. Both active substances are described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice. The CEP procedure is used for both active substances.

The active substance specification is considered adequate to control the quality of the active substances. Information and documentation of the micronisation sites has been provided for both active substances as the micronisation step is not covered by the different CEP's.

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

E. Control tests on the finished product

The finished product specification controls the relevant parameters for the pharmaceutical form. The proposed limits are acceptable.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specification.

A Risk Assessment on elemental impurities has been submitted for the proposed product. Compliance with the ICH Q3D has been demonstrated. No risk on elemental impurities is expected.

F. Stability tests

The information on retest period and container closure is as per CEP's of the active substance and, hence, the information is accepted.

The stability conditions and data provided for the finished product are acceptable as per VICH GL3 and applicable European guidelines, including the proposed bracketing approach.

Based on the stability results provided, the proposed shelf-life of 21 months is acceptable when stored under the approved conditions. The proposed storage claim "Do not store above 25°C. Store in the original package to protect from light" is accepted.

3. SAFETY DOCUMENTATION (safety and residues tests)

Milpro Chewy 2.5 mg / 25.0 mg chewable tablets and Milpro Chewy 12.5 mg / 125.0 mg chewable tablets: As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has been demonstrated, results of safety tests are not required.

Milpro Chewy 25.0 mg / 250.0 mg chewable tablets: As this is a hybrid application according to Article 19 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has been demonstrated, results of safety tests are not required

The safety aspects of this VMP are identical to the reference VMP.

Warnings and precautions as listed on the product literature are the same as those of the reference VMP and supplemented with additional statements, based on increased knowledge and the current state of science. This information is considered adequate to ensure safety of the product to users and the environment.

A. Safety tests

Pharmacological studies

The applicant provided bibliographical data which substantiates the information as presented in section 4.2 and 4.3 of the SPC.

Toxicological studies

As this is an application submitted in accordance with article 18 and 19 of Regulation (EU) 2019/6, and bioequivalence with a reference VMP has been demonstrated, results of safety tests are not required. Nevertheless the applicant has provided toxicity data and the underlying bibliographical documentation.

User safety

The applicant has provided a user safety assessment in compliance with the relevant guideline and acknowledges the risk of accidental ingestion by children. Furthermore the risk of hypersensitivity to butylhydroxyanisole, macrogols or soya (bean) oil was addressed.

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.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

Milpro Chewy 2.5 mg / 25.0 mg chewable tablets and Milpro Chewy 12.5 mg / 125.0 mg chewable tablets: As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has been demonstrated, efficacy studies are not required. The efficacy claims for this VMP are equivalent to those of the reference VMP.

Milpro Chewy 25.0 mg / 250.0 mg chewable tablets: As this is a hybrid application according to Article 19 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has been demonstrated, efficacy studies are not required.

The efficacy claims for this VMP are equivalent to those of the reference VMP.

A. Pre-Clinical Studies

Bioequivalence was demonstrated with a preliminary bioequivalence study (which provided information in terms of optimising the sampling schedule and sample size calculation for the pivotal field study) as well as a Pivotal bioequivalence study conducted with the 12.5 mg / 125.0 mg chewable tablets.

The bioequivalence study has been conducted with one batch of the Medium strength of the test product vs one batch of the Medium strength of the reference product. For the Small and Large strengths, a biowaiver of strength has been requested. The dissolution conditions used for the biowaiver of strength are acceptable. The biowaiver of strength has been adequately demonstrated for the Small and the Large strengths at 3 different pH's. The comparative dissolution profile testing has been undertaken on three production batches per strength.

Pharmacology

The applicant provided bibliographical data which substantiates the information as presented in section 4.2 and 4.3 of the SPC

Development of resistance and related risk in animals

The bibliography / information provided suggests that in third countries (USA), resistance of *Dipylidium caninum* to praziquantel as well as cases of multiple-drug resistance of *Ancylostoma caninum* and resistance of *Dirofilaria immitis* to macrocyclic lactones have already been reported.

Adequate warnings and precautions appear on the product literature.

Tolerance in the target species of animals

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

B. Clinical trials

No clinical trials were performed as bioequivalence with the reference products has been demonstrated by means of an *in vivo* bioequivalence study and *in vitro* dissolution studies.

A palatability study was performed and the data suggest a comparable consumption for reference and candidate product.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP is 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 VMP for humans and the environment is acceptable.

POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the VMP. The current SPC is available in the Union Product Database (UPD).

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 VMP.

None.