College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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The Netherlands

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Alpramil 5 mg/50 mg tablets for dogs weighing at least 0.5 kg
Alpramil 12.5 mg/125 mg tablets for dogs weighing at least 5 kg
Alpramil 20 mg/200 mg tablets for dogs weighing at least 8 kg

PRODUCT SUMMARY

EU procedure number	NL/V/0364/004-006/DC
Name, strength and pharmaceutical form	Alpramil 5 mg/50 mg tablets for dogs weighing at least 0.5 kg Alpramil 12.5 mg/125 mg tablets for dogs weighing at least 5 kg Alpramil 20 mg/200 mg tablets for dogs weighing at least 8 kg
Applicant	Alfasan Nederland B.V. Kuipersweg 9 3449 JA Woerden The Netherlands
Active substance(s)	Milbemycin oxime and Praziquantel
ATC vetcode	QP54AB51
Target species	Dog
Indication for use	Treatment of mixed infections by adult cestodes and nematodes of the following species susceptible to praziquantel and milbemycin oxime: - 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 section “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.

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*	Alpramil 12.5 mg/125 mg: Generic application made in accordance with Article 13(1) of Directive 2001/82/EC Alpramil 5 mg/50 mg and Alpramil 20 mg/200 mg: Hybrid application made in accordance with Article 13(3) of Directive 2001/82/EC
Reference product (RP)	Milbemax 12.5/125 tablets for dogs
Marketing authorisation holder	Elanco GmbH
MS where the RP is or has been authorised	
Marketing authorisation number EU procedure number	REG NL 10091, FR/V/0135/002
Date of authorisation	8 July 2003
Date of completion of the original decentralised procedure	9 February 2022
Date veterinary medicinal product first authorised in the Reference Member State (MRP only)	
Concerned Member States for original procedure	BE, BG, CY, CZ, DE, EE, EL, ES, FI, FR, HU, HR, IE, IS, IT, LT, LU, LV, NO, PL, PT, RO, SI, SK, UK(NI)
Concerned Member States for subsequent recognition procedure	
Withdrawn CMS during original decentralised procedure	AT, SE, DK: The company decided to withdraw the application. At the time of withdrawal, the MS considered that the data provided did not allow to conclude on a positive benefit-risk balance as potential serious risk to public health was raised.

*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 tablets contain resp. 5/50 mg; 12.5/125 mg; 20/200 mg Milbemycin oxime /Praziquantel. and the following core excipients: Povidone, Cellulose, microcrystalline, Croscarmellose sodium, Lactose monohydrate, Silica, colloidal hydrated, Magnesium stearate, Chicken flavour and Yeast (dried)
The 5/50 mg tablet is cross scored and meant to be broken into equal halves or quarters.
The products are packed in OPA/aluminium/PVC-aluminium blister packs, containing 1, 2 or 4 tablets.

The VMP is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

A bioequivalence study is performed with the 12.5/125 mg tablet strength and the other strengths are waived.

B. Description of the manufacturing method

The VMP is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

The VMP is manufactured using conventional manufacturing techniques. Since the tablets contain the active substance milbemycin oxime in a low content (≤ 2%) it should be considered as a non-standard process. However, concerning the extensive experience of the finished product manufacturer in producing tablets containing low contents of active substance the manufacturing process is considered a standard process.
The tests performed during production are described.

C. Production and control of starting materials

The active substances is milbemycin oxime for veterinary us and praziquantel are established active substances described in the European Pharmacopoeia. Milbemycin oxime is manufactured at Hubei Honch Pharmaceutical Co., Ltd. Praziquatel is manufactured at Alivira

Animal Health Limited. Both active substances are manufactured in accordance with the principles of good manufacturing practice.

CEP procedures have been employed. Regarding praziquatel a copy of the current CEP should be submitted.

The active substance specification is considered adequate to control the quality of the material from the supplier. Batch analytical data demonstrating compliance with this specification have been provided.

All excipients are in conformity with the Ph.Eur. requirements with the exception of the Yeast and Chicken flavour which have been adequately specified.

The packaging is conformity with the EU Food Directive.

Both lactose monohydrate and chicken flavour contain materials of animal origin but give no potential risk of transmitting animal spongiform encephalopathy agents

D. Control tests carried out on isolated intermediates during the manufacturing process

Not applicable

E. Control tests on the finished product

The finished product specification controls the relevant parameters for the pharmaceutical form.

Relevant 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.

F. Stability tests

According to the claims on the CEP's for milbemycin oxime for veterinary use a retest period of 36 months and for praziquantel can be granted

Stability data on the finished product has been provided in accordance with applicable European guidelines. According to the stability results provided the claimed shelf life of 24 months can be granted.

G. Other information

Not applicable

3. SAFETY DOCUMENTATION (safety and residues tests)

Alpramil 12.5 mg/125 mg: As this is a generic application made in accordance with Article 13(1) of Directive 2001/82/EC and essential similarity to a reference VMP has been demonstrated, results of safety tests are not required.

Alpramil 5 mg/50 mg and Alpramil 20 mg/200 mg: As this is a hybrid application made in accordance with Article 13(3) of Directive 2001/82/EC and essential similarity to 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

User safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.

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)

Alpramil 12.5 mg/125 mg: As this is a generic application made in accordance with Article 13(1) of Directive 2001/82/EC and essential similarity to a reference VMP has been demonstrated, results of safety tests are not required.

Alpramil 5 mg/50 mg and Alpramil 20 mg/200 mg: As this is a hybrid application made in accordance with Article 13(3) of Directive 2001/82/EC and essential similarity to a reference VMP has been demonstrated, results of safety tests are not required.

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

A pilot and pivotal *in vivo* bioequivalence study, using a validated LC/MSMS method for sample analysis, with the 12.5/125 mg strength of both the reference product and the product

applied for was conducted. The studies demonstrated a very similar pharmacokinetic profile for both test and reference product, bioequivalence was demonstrated for the pivotal parameter AUC. For Cmax a (slight) increase of the upper bounds (1.30 for Milbemycin and 1.34 for Praziquantel) were observed. The applicant provided a literature overview to substantiate the safety of the VMP and it was concluded that no safety concerns exist in relation to the observed (slight) increase of the upper bounds for Cmax.

The *in-vivo* essential similarity demonstrated between the test product and reference product for the 12.5/125mg strength was extrapolated to the other strengths based on dissolution testing.

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