MINISTERIO
DE SANIDAD, CONSUMO
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agencia española de
medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

DRAFT PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

CANIHELMIN PLUS 50 mg/144 mg/150 mg tablets for dogs

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0245/001/DC
Name, strength and pharmaceutical form	Canihelmin plus 50 mg/144 mg/150 mg tablets for dogs
Applicant	GENERA Inc. Svetonedeljska 2, Kalinovica 10436 Rakov Potok Croatia
Active substance(s)	Praziquantel Pyrantel Embonate Febantel
ATC Vet code	QP52AA51
Target species	Dogs
Indication for use	Treatment of mixed infections by nematodes and cestodes of the following species: <u>Nematodes:</u> **Ascarids:** *Toxocara canis*, *Toxascaris leonina* (adults). **Hookworms:** *Uncinaria stenocephala*, *Ancylostoma caninum* (adults). **Whipworms:** *Trichuris vulpis* (adults). <u>Cestodes:</u> **Tapeworms:** *Echinococcus* spp (*Echinococcus granulosus, Echinococcus multilocularis*), *Taenia* spp. (*Taenia hydatigena, Taenia pisiformis, Taenia taeniaeformis*),*Dipylidium caninum (adults).*

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application under Article 12(3) (known active substance) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	28 April 2016
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	BG, CZ, DE, IE, PL, RO, UK

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 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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains praziquantel (50 mg/tablet), pyrantel (50 mg/tablet) and febantel (150 mg/tablet) and the excipients Lactose monohydrate, Maize starch, Copovidone, Sodium laurilsulfate, Cellulose microcrystalline, Silica, colloidal anhydrous, Hydrogenated vegetable oil type I, Talc and Magnesium stearate

The container/closure system is Al-PE/Al-PE strips.

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 from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substances are praziquantel, pyrantel embonate and febantel. These active substances are described in the European Pharmacopoeia and are manufactured in accordance with the principles of good manufacturing practices.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided and 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 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 have been provided.

Batch analytical data from the proposed production site have 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 substance when stored under the approved conditions.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data of each active substance.

Pharmacodynamics

Praziquantel
The active substance is a pyrazinoisoquinoline which causes paralysis of the target parasite, leading to death.

Pyrantel
The active substance is an imidazothiazole derivative, which acts by causing a neuromuscular block within the nicotinic receptors of the target parasite.

Febantel
The active substance is a probenzimidazole, which acts by binding to tubulin, with resulting interference to the cell membrane and microtubule structure, while also affecting glucose metabolism and transport.

Pharmacokinetics

Praziquantel is quantitatively and rapidly absorbed and metabolized by all species. All species excrete the parent compound and its metabolites rapidly. Renal excretion is the main route of elimination of praziquantel and its metabolites.

The pyrantel embonate is poorly absorbed from the gastro-intestinal tract and absorbed drug is rapidly metabolized and excreted into the feces.

Febantel is absorbed from the intestinal tract, metabolized in the liver, and eliminated- up to 70% - by the bile at a half-life of 9 h in rats. Febantel is quickly metabolized to fenbendazole.

Toxicological Studies

The applicant has provided bibliographical data.

- Single Dose Toxicity: All three active substances are of low toxicity. The LD_{50} in dogs is > 690 mg/kg (pyrantel palmitate) and > 10.000 mg/kg (febantel). An acute, oral LD50 has not been established in dogs because they vomit when dosages exceed 200 mg/kg.

- Repeated Dose Toxicity: From published studies, it was noted that toxicity was minimal on repeat dosing in dogs

- Reproductive Toxicity, including Teratogenicity: From published studies, it was noted that no effect was seen on reproduction in dogs

- Mutagenicity: From published studies, it was noted that no mutagenic effect was seen in dogs

- Carcinogenicity (if necessary): From published studies, it was noted that no carcinogenic effect was seen in dogs

Observations in Humans

From published data submitted, it was noted that praziquantel and pyrantel are used in human medicine, with no significant side effects observed. Febantel is not used in human medicine.

Excipients are commonly used in oral pharmaceutical products for both humans and animals.

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 product.

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines. The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food animals.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Not applicable

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data to characterise the pharmacodynamic effects of each component. The combination is justified by the prevalence of mixed infections o**f** roundworms and cestodes in dogs and puppies. There are extensive bibliography addressing the pharmacodynamic features of combination.

Omission of data on pharmacokinetics for this fixed combination was justified on basis that of the low biodisponibility of pyrantel and febantel. Only measurable pharmacokinetic parameters have been obtained for praziquantel.

Tolerance in the Target Species of Animals

The applicant has provided target animal tolerance data from confirmation dose studies and field trial studies using the recommended dose in the target species. Bibliographical data and post marketing information have also been provided which shows that all adverse reactions detected are those consigned at relevant SPC section. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

No resistance evidence have been notified to the combination along the time.
Adequate warnings and precautions to minimize resistance to the treatment appear on the product literature.

IV.B Clinical Studies

It was carried out three proprietary clinical trials, one was with artificially infected dogs and another two ones were on naturally infected dogs. Based on these three clinical studies no significant adverse events were registered.

Laboratory Trials

The applicant has conducted a dose confirmation study which show efficacy of a single treatment of 5 mg/kg for PRZ, 14.4 mg/kg for PYR and 15 mg/kg for FEB on adequately *Echinococcus granulosus* artificially infected dogs.
The trial was designed as a laboratorial uni-centric, negative controlled non-blinded field trial.
Parasite count after a single treatment with the test product shows a 100% success rate was achieved for *Echinococcus granulosus* infestation.
Euthanasia was done after treatment; the small intestine was separated for tapeworm count. Number of found tapeworms were compared with the findings in the control group. Safety measures were be taken for corpses disposal. Health status of dogs were recorded daily, no adverse signs were recorded along the study that could be attributed to the administration of the medicinal product.

Field Trials

Two field trials were submitted.

The first one, was designed as a uni-centre, self controlled (critical test) non-blinded field trial to evaluate the efficacy of the test product against natural infections of *Toxocara canis*, *Ancylostoma caninum* and *Trichuris vulpis*. A suitable number of dogs chosen based on the results of coprological findings (for presence and identification of nematodes searched), were given the recommended dose.

Efficacy was assessed on egg burden reduction respect previous counts before treatment and significance determined by Student Test (within the group). It is a critical test with no negative infected control group.

Results can be summarised as parasite egg counts before and after a single treatment with the test product showed a 100% success rate that was achieved for *Ancylostoma caninum* and *Toxocara canis* infestation. For *Trichuris vulpis* reduction egg count was lower, around 95%, being higher at a second coprological analysis after treatment.

This study is carried out under VICH GL19 principles; the faecal egg count on coprological analyses is suitable efficacy analysis for this combination of well known combination of substances. Results obtained higher than 90 % is in line or required in this guideline and so is the lapsus of time when the coprological analysis were made (10 and 15 days after treatment).

A second study was designed as unicentric, positive controlled field trial, to assess the efficacy of product in treatment of tapeworms and nematodes in naturally infected dogs.

Following results after treatment were recorded:
- For tapeworms and for *Toxocara canis* a 100% of reduction of the infection burden was achieved with both treatments.
- For hookworms infection 99.76% and 99.64% of reduction in faecal eggs counts was measured for reference and test product respectively.
- For whipworms infection, 97.16% and a 97.80% of reduction in faecal eggs counts was measured for reference and test product respectively.

The global egg reduction for the reference product caused a 99.37
% reduction while for The test product was for 99.32 %.
A macroscopic and a microscopic analysis of faeces for faecal eggs counts were made 7 days after treatment. Egg counts was made by a WAAVP and VICH recommended method.

Parasite egg count before and after a single treatment with test product shows a 100% success rate and it was achieved for *Ancylostoma caninum* and *Toxocara canis* infestation. For *Trichuris vulpis* reduction egg count was lower, around 95%. Being higher at second coprological analysis after treatment. Similar results were obtained for treatment with reference product.

The study is carried out under VICH GL19, the egg count on coprological analyses is suitable efficacy analysis for this combination of well known combination of substances. The results obtained higher than 90 % is in line or required in this guideline and so in the lapsus of time when the coprological analysis were made (7 days after treatment).

In addition extensive bibliography has been submitted in support of the efficacy of all three active substances when used individually or in combination. Based on the bibliographic data presented, the proposed doses for each of the actives, whether used alone or in combination, are justified. Further, administration of the combination can be expected to be efficacious against the claimed target parasites.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

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 veterinary Heads of Agencies website (www.hma.eu).

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.

None