United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey
KT15 3LS
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Anthelmin Plus Flavour Tablets for Dogs (BE, IE, IT, NL, UK)
Dehinel Plus Flavour Tablets for dogs (BG)
Zikyall Sabor Tablets for dogs (ES, PT)
Anthelmin vet 150 mg/144 mg/50 mg tablets for dogs (FI)

Anthelmin Plus XL Tablets for Dogs
Dehinel Plus XL Tablets for dogs (BG)
Zikyall Tablets for large dogs (ES, PT)
Anthelmin vet 175 mg/504 mg /525 mg tablet for dogs (FI)

PuAR correct as of 26/10/2018 when RMS was transferred to IE.
Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0340/001/E/001 UK/V/0340/002/E/001
Name, strength and pharmaceutical form	Anthelmin Plus Flavour Tablets for Dogs Anthelmin Plus XL Tablets for Dogs
Applicant	KRKA d.d, Novo mesto Šmarješka cesta 6 8501 Novo mesto Slovenia
Active substance(s)	Praziquantel, pyrantel embonate, febantel
ATC Vetcode	QP52AC55
Target species	Dogs
Indication for use	For the treatment of mixed infestations with the following roundworms and tapeworms in adult dogs (and puppies, Anthelmin Plus Flavour Tablets for Dogs only): Nematodes Ascarids: *Toxocara canis*, *Toxascaris leonina* (late immature forms and mature forms) Hookworms: *Uncinaria stenocephala*, *Ancylostoma caninum* (adults) Cestodes Tapeworms: *Taenia* spp., *Dipylidium caninum*

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	22nd January 2015
Date product first authorised in the Reference Member State (MRP only)	24th November 2010
Concerned Member States for original procedure	Belgium, The Netherlands Concerned Member States added for Repeat Use Procedure: Bulgaria, Finland, Ireland, Italy, Portugal, Spain.

I. SCIENTIFIC OVERVIEW

These were generic applications submitted in accordance with Article 13 (1) of Directive 2001/82/EC). The reference product for Anthelmin Plus Flavour Tablets for Dogs is Drontal Plus Flavour Tablets. The reference product for Anthelmin Plus XL Tablets for Dogs is Drontal Plus XL Tablets. Both reference products have been marketed since 1993.

Anthelmin Plus Flavour Tablets for Dogs and Anthelmin Plus XL Tablets for Dogs are intended for the treatment of mixed infestations with roundworms and tapeworms in dogs. Anthelmin Plus Flavour Tablets for Dogs may be used in small and medium sized dogs and puppies, the tablets may be divided into equal halves or quarters. Anthelmin Plus XL Tablets for Dogs may be used in large and extra-large sized dogs, and can be divided into equal halves. The products may be used to treat: nematodes *Toxocara canis*, *Toxascaris leonina* (late immature forms and mature forms), hookworms *Uncinaria stenocephala*, *Ancylostoma caninum* (adults), and tapeworms (cestodes) *Taenia spp*., and *Diplydium caninum.*

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[1]. 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.

[1] Summary of Product Characteristics

II. QUALITY ASPECTS

A. Composition

Anthelmin Plus Flavour Tablets for Dogs contain 50 mg praziquantel, 144 mg pyrantel embonate and 150 mg febantel per tablet. Anthelmin Plus XL Tablets for Dogs contain 175 mg praziquantel, 504 mg pyrantel embonate and 525 mg febantel per tablet. The excipients are lactose monohydrate, maize starch, povidone k-30, sodium lauryl sulphate, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate. Anthelmin Plus Flavour Tablets for Dogs also contain meat flavour.

The container/closure system is a print perforated aluminium-aluminium blister with a folding box as an outer package. Anthelmin Plus Flavour Tablets for Dogs are available in 2, 4, 10, 30, 50, 100 or 300 tablets. Anthelmin Plus XL Tablets for Dogs are available in 2, 4, 10, 12, 24, 30, 50, 60, 100 or 102 tablets. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified.

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.

Manufacturing formulae for varying batch sizes were provided. The active substances along with lactose monohydrate and maize starch are sieved and granulated. A binding solution is prepared by the addition of povidone and sodium lauryl sulphate in water, and the solution is added to the dry mixture of the other ingredients, and if necessary, additional water. The product is dried and mixed with the remaining excipients prior to compression. Process validation was performed on two commercial scale batches. Analyses were made on loss of product on drying and on compression. During tablet formation, the product was checked for appearance, mass variation, thickness and disintegration time. The content of the active substances was also monitored.

C. Control of Starting Materials

The active substances are praziquantel, pyrantel embonate and febantel, established active substances. 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.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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

E. Control on intermediate products

There are no intermediate products.

F. 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 sites have been provided demonstrating compliance with the specification. The finished product is analysed with regard to: appearance, uniformity of dosage units, water, uniformity of mass of sub-divided tablets, identification of active substances, related substances, dissolution and microbial quality.

G. 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. The re-test periods are as follows: febantel 2 years, praziquantel 5 years and pyrantel embonate 3 years.

Stability data on the finished products 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. Data were provided on the finished product, stored as proposed for commercial use. The study was conducted for up to 6 months at accelerated conditions, (40^{o}C/75%RH), and additionally for 6 months under long term conditions at 25^{o}C/60%RH. Another batch was stored for 9 months long term. Parameters analysed were water content, appearance, content of active substances, dissolution, microbiological quality and degradation products. All results were satisfactory.

The shelf-life of the products as packaged for sale is 3 years.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

The shelf-life of the products as packaged for sale is 3 years. The products do not require any special storage conditions.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As these were generic applications according to Article 13 (1), and bioequivalence with a reference product has been demonstrated, results of pharmacological and toxicological tests are not required. Under the current Requirement for Anthelmintics, bioequivalence can be demonstrated by the use of clinical equivalence studies rather than by plasma pharmacokinetics. Assuming bioequivalence with the reference products, there was no requirement for data in this section.

The safety aspects of these products are identical to the reference products.

Warnings and precautions as listed on the product literature are the same as those of the reference products and are adequate to ensure safety of the product to users and the environment.

III.A Safety Testing

Pharmacological Studies

Under the current Requirement for Anthelmintics, bioequivalence can be demonstrated by the use of clinical equivalence studies rather than by plasma pharmacokinetics. Assuming bioequivalence with the reference products, there was no requirement for data in this section.

Other Studies

Under the current Requirement for Anthelmintics, bioequivalence can be demonstrated by the use of clinical equivalence studies rather than plasma pharmacokinetics. Assuming bioequivalence with the reference products, there was no requirement for data in this section.

User Safety

A user risk assessment was provided. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. The following safety warnings were proposed:-

- In the interests of good hygiene, persons administering the tablet directly to a dog or by adding it to the dog's food should wash their hands afterwards.
- In case of accidental ingestion, seek medical advice and show the package leaflet to the physician.

The warnings are identical to those of the reference products.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The assessment concluded that no extensive exposure of the environment would occur due to use of the products, and this was acceptable

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

Residue Studies

Not applicable in a non-food producing species.

IV CLINICAL ASSESSMENT (EFFICACY)

As these were generic applications according to Article 13 (1), and bioequivalence with the reference products was claimed, efficacy studies were not required. The efficacy claims for these products are equivalent to those of the reference products. Data from appropriate dissolution studies were analysed in order to extrapolate similarity of bioavailability between the two different sized products. Results were satisfactory.

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

As these were generic applications according to Article 13 (1), and bioequivalence with the reference products was effectively claimed, tolerance studies were not required. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

As these were generic applications according to Article 13 (1), and bioequivalence with the reference products was effectively claimed, resistance studies were not required.

IV.B Clinical Studies

A series of references and other supporting data were submitted in support of the use of the active substances. A large number of references were provided

for praziquantel, and suitable justification was provided retrospectively for the omission of plasma bioequivalence studies for febantel and pyrantel embonate.

Praziquantel is thought to interact with voltage-gated Ca^{2+} channels in the gut lumen of parasites, causing an influx of Ca^{2+} ions leading to the spastic paralysis of the parasite. In addition, parasite-related immunological epitopes are exposed, leading to attack on the parasite by the host's immune system. Radiolabelled praziquantel has been shown to become rapidly and almost completely absorbed between 30 and 60 minutes after administration. Less than 1% of the administered dose enters the systemic circulation, with approximately two thirds of the active substance being excreted by the kidneys.

The results of several studies were provided investigating the efficacy of combination products against a variety of parasites.

Dose confirmation studies were performed using Dehinel Plus Flavoured Tablets, (identical to Anthelmin Plus Flavour Tablets for Dogs), containing the named active substances in the specified amounts.

An initial study evaluated Dehinel Plus Flavour Tablets versus Drontal Plus Flavour Tablets against *Diplydium caninum* in naturally infected dogs. A suitable number of animals, naturally infected with *Diplydium caninum* were divided into groups with regard to gender and bodyweight. This was a single centre, randomised, parallel arm, blinded and controlled study. On day 7, all animals were treated for flea infestations which could permit reinfection with *D. Caninum*. Animals were dosed with product or reference product on confirmation of infection, at a dose of 1 tablet per 10 kg body weight. All animals were monitored throughout the procedure, and examined at necropsy. Both tablets proved 100% effective at removing the target organism.

Additional studies were performed in order to test the efficacy of the product against other parasites: Dehinel Plus Flavour Tablets and Drontal Plus Flavour Tablets against *Tania hydatigena*, (effective), Dehinel Plus Flavour Tablets and Drontal Plus Flavour Tablets against *Ancyclostoma caninum* and *Uncinaria stenocephalus*, (effective), Dehinel Plus Flavour Tablets and Drontal Plus Flavour Tablets against *Toxocara canis*, (effective).

Suitable dissolution data were provided to ensure that data could be extrapolated for Anthelmin Plus Flavour Tablets and Drontal Plus Flavour Tablets to Anthelmin Plus XL and Drontal Plus, and between flavoured and non-flavoured tablets.

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.

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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)