Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Dinelix Plus Tablets for Dogs
Praziworm Plus Tablets for Dogs
Voxical Plus Tablets for Dogs

Date Created: March 2021

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Dinelix Plus Tablets for Dogs Praziworm Plus Tablets for Dogs Voxical Plus Tablets for Dogs
Applicant	C&H Generics Ltd C/o Michael McEvoy and Co Seville House New Dock Street Galway Ireland
Active substance	Pyrantel embonate Praziquantel Febantel
ATC Vetcode	QP52AA51
Target species	Dogs
Indication for use	For the treatment of mixed infections with roundworms, hookworms, whipworms, and tapeworms of the following species: **Roundworms (Nematodes):** Ascarids (adult and late immature forms): *Toxocara canis*, *Toxascaris leonina*. Hookworms (adults): *Uncinaria stenocephala*, *Ancylostoma caninum*. Whipworms (adults)**:** *Trichuris vulpis*. **Tapeworms (Cestodes):** Adult and immature forms of: *Echinococcus* species *(E. granulosus, E. multilocularis), Taenia* species *(T. hydatigena, T. pisiformis, T. taeniformis), Dipylidium caninum*.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic 'hybrid' applications in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	12/01/2021

I. SCIENTIFIC OVERVIEW

These were applications for 'hybrid' products, submitted under Article 13 (3) of Directive 2001/82/EC as amended. These were determined to be generic 'hybrid' applications, because bioequivalence could not be demonstrated or inferred through bioavailability studies, due to limited systemic absorption. The reference product is Drontal Plus Bone Shaped Flavour Tablets (now Bob Martin 3 in 1 Dewormer Tablets), which has been authorised in the UK since June 1989. The dossiers were previously assessed under a Mutual Recognition Procedure for Prazitel Plus Tablets, authorised in the UK in December 2009, and previously submitted via national procedures for the Extrontel/Ezi-Wormer/Molecare/Rofectan Plus range of products in March 2012 and 2015. Data for the current applications were previously assessed for these products.

The products contain 144 mg pyrantel embonate, (equivalent to 50 mg pyrantel), 50 mg praziquantel, and 150 mg febantel per tablet. The proposed indication is for treatment of mixed infections with roundworms: ascarids (adult and late immature forms): *Toxocara canis*, *Toxascaris leonina* Hookworms: (adults) Unicinaria stenocephala, *Ancylotoma caninum*, whipworns: (adults) *Trichuris vulpis*, and tapeworms, adult and immature forms of: *Echinococcus* species *(E. granulosus, E. multilocularis), Taenia* species *(T. hydatigena, T. pisiformis, T. taeniformis),* and *Dipylidium caninum,* in dogs.

The recommended dose is 1 tablet per 10 kg (22 lbs) bodyweight. This is equivalent to 15 mg febantel, 14.4 mg pyrantel embonate and 5 mg praziquantel per kilo bodyweight, as a single oral administration.

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, any 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 [2] of the product was demonstrated

[1] SPC – Summary of product Characteristics.

according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains pyrantel embonate, febantel and praziquantel, and the excipients as follows: lactose monohydrate, microcrystalline cellulose, magnesium stearate, colloidal anhydrous silica, croscarmellose sodium, sodium laurilsulfate and pork flavour.

The container/closure system consists of individual strips composed of aluminium foil 30 µm with 30 gsm extruded polythene, containing 1, 2, 4, 6, or 8 tablets. Or, individual blisters composed of 45 µm, soft temper aluminium foil and 25 µm hard temper aluminium foil, containing 1, 2 or 8 tablets.

The strips or blisters are packed into cartons containing either 1, 2,4, 6, or 8 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.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from licensed manufacturing sites. The manufacturing method consists of the dissolution and addition of components, sifting, and compression, followed by packaging of the products.

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

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

II.C. Control of Starting Materials

The active substances are pyrantel embonate, praziquantel and febantel, established active substances described in the European Pharmacopoeia (Ph.

[2] Efficacy – The production of a desired or intended result.

Eur). 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. Acceptable Certificates of Suitability were provided.

All excipients are described in the Ph, Eur, apart from pork flavour, for which acceptable documentation was provided.

Packaging complies with Ph. Eur monographs or relevant specifications.

II.C.4. Substances of Biological Origin

The suppliers of the active substances have provided declarations that their materials are not derived from materials of animal origin and no intermediates or auxiliary agents are used in the manufacturing process.

The supplier of lactose monohydrate has certified that the milk used for production of lactose derives from healthy animals and is collected as milk for human consumption and that the lactose is prepared without the use of other ruminant materials than milk and calf rennet.

The supplier of magnesium stearate has certified that their material is of vegetable and mineral origin.

The suppliers of the other excipients (microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, sodium laurilsulfate and pork flavour) have provided declarations that their materials are free from TSE risk material.

The applicant has submitted satisfactory EMA Tables regarding materials of animal and human origin.

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. 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. Control tests on the

finished product are those for: appearance, identification of active substances and components, weight, dissolution and microbial purity.

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 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

Shelf life of the veterinary medicinal product as packaged for sale: 5 years. Discard any divided tablets.

This veterinary medicinal product does not require any special temperature storage restrictions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

The applicant states that the products are quantitatively and qualitatively similar to the reference product. A bioequivalence study comparing the reference product with the proposed product was submitted, which is reported in Part IV. Claims have been made that bioequivalence to the reference product has been demonstrated and therefore no pharmacological or toxicological data were submitted. A user safety risk assessment and environmental risk assessment were submitted.

III.A Safety Documentation

User Safety

A user risk assessment was provided 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. Therefore, the following applicant's user recommendations are appropriate:

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

Other precautions

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.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

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.

Residue Studies

No residue depletion studies were conducted due to the nature of the application, which is for a tablet in non-food producing animals.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

the following was claimed by the applicant with regard to reference and proposed products:

> Both products are of the same qualitative and quantitative composition in terms of active substances, containing 144 mg of pyrantel embonate, (equivalent to 50 mg pyrantel), 50 mg praziquantel and 150 mg febantel per tablet.
>
> The two products are of the same pharmaceutical form, tablets for oral administration.
>
> The products can be considered bioequivalent.

Pharmacodynamic tests were not required.

Pharmacokinetics

A bioequivalence study comparing the reference and proposed products was submitted. This was a two treatment, two period, randomised crossover study, with 12 dogs per study group. The animals were administered with either product, according to bodyweight, and then with the alternate product after the 21 day washout period. Blood tests were taken at appropriate time points. No adverse reactions occurred due to administration of the products. Bioequivalence was partially confirmed by the study, due to the nature of the products, but it was noted that:

- *The test and reference products can be considered equivalent with respect to systemic availability (AUC_{inf}) of praziquantel.*

- *The test product can be considered more bioavailable than the reference product with respect to pyrantel, febantel, fenbendazole and oxfendazole.*

Acceptably widened acceptance limits were permitted and justified where appropriate. Along with a dissolution study which successfully compare the proposed product with the reference product, and published literature as further supporting data, bioequivalence was accepted, taking all the data into account.

Tolerance in the Target Species

The proposed and reference product were considered essentially similar. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

Resistance in relation to the proposed product is considered to be no different to that of the reference product. Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Due to the nature of the applications and the data provided, no further assessment was 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 of the products is favourable.

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)