Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Quantilex Plus Tablets for Dogs

Date Created: December 2015

PuAR correct as of 12/03/19 when RMS was transferred to CZ.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0582/001/MR
Name, strength and pharmaceutical form	Quantilex Plus Tablets for Dogs
Applicant	Chanelle Pharmaceutical Manufacturing Ltd. Loughrea, Co. Galway Ireland
Active substance(s)	Praziquantel, pyrantel, febantel
ATC Vetcode	QP52AA51
Target species	Dogs
Indication for use	In dogs: Treatment of mixed infections by nematodes and cestodes of the following species **Nematodes:** **Ascarids:** *Toxocara canis*, *Toxascaris leonina* (adult and late immature forms). **Hookworms:** *Uncinaria stenocephala*, *Ancylostoma caninum* (adults). **Whipworms:** *Trichuris vulpis* (adults). **Cestodes:** **Tapeworms:** *Echinococcus* species, *(E. granulosus, E. multilocularis), Taenia* species, *(T. hydatigena, T. pisiformis, T. taeniformis), Dipylidium caninum* (adult and immature forms).

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' application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition	24th August 2015
Date product first authorised in the Reference Member State (MRP only)	28th August 2012
Concerned Member States for original procedure	Czech Republic, Slovakia

I. SCIENTIFIC OVERVIEW

This was a generic 'hybrid' application, in accordance with Directive 2001/82/EC as amended. Bioequivalence was supported by proprietary data and published literature, as bioequivalence was not obtained for all relevant parameters. The reference veterinary medicinal product is Drontal Plus, which has been authorised in the UK for more than 10 years, now called Bob Martin 3 in 1 Dewormer Tablets for Dogs.

The product is indicated for use in dogs, for the treatment of mixed nematode and cestodes infections of the following species: *Toxocara canis, Toxascaris leonina* (adult and late immature forms0, hookworms *Uncinaria stenocephala* and *Ancylostoma canimum* (adults). Whipworms Trichuris vulpis (adults), Tapeworms *Ecchinococcus granulosus, E. Multilocaris* and *Taenia* species, *T. Hydatigena, T. Pisiformis, T. Taeniformis*, also, *Diplydium canimum* (adult and immature forms).

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] SPC – Summary of Product Characteristics.

II. QUALITY ASPECTS

A. Composition

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

The container/closure system consists of individual strips of blisters of soft tempered aluminium foil and hard tempered foil for 2 or 8 tablets. The blisters are packed into cartons containing varying numbers of tablets: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 30, 32, 36, 40, 42, 44, 48, 50, 52, 56, 60, 70, 80, 84, 90, 98, 100, 104, 106, 120, 140, 150, 180, 200, 204, 206, 250, 280, 300, 500 or 1000 tablets. Or, individual strips composed of aluminium foil and extruded polythene, containing 2, 4, 6, 8, 10, 12, 14, 16, 18 or 20 tablets. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and 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. Process validation data on the product have been presented in accordance with the relevant European guidelines. The manufacturing process consists of a standard wet granulation and compression technique, with the active substances being granulated with a portion of the excipients before drying, and the addition of remaining excipient. Compression then takes place, followed by packing.

C. Control of Starting Materials

The active substances are praziquantel, febantel and pyrantel embonate, established substances described in the European Pharmacopoeia (PH. Eur). The active substance is 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

Compliance with the Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Veterinary Medicinal Products is addressed as outlined below:

- The suppliers of the active substances have provided declarations that their materials are not derived from 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". This is considered adequate as these types of products are excluded from the guideline.

- 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 lauryl sulphate and pork flavour) have provided declarations that their materials are free from TSE risk material.

A Format 2 declaration was included.

E. Control on intermediate products

Not applicable.

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 site have been provided demonstrating compliance with the specification. Tests include those for appearance, identification of active substances, weight, friability, hardness, moisture, dissolution, uniformity of dose and microbial purity.

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.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years
Discard any unused divided tablets.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This was a generic 'hybrid' application according to Article 13 (3). Differences in the product formulation from that of the reference product required the submission of pharmacological and toxicological data relevant to the User Risk Assessment, including formulation specific data. Warnings and precautions as listed on the product literature are adequate to ensure safety of the product to users and the environment.

III.A Safety Testing

Pharmacological Studies

A large number of studies were submitted by the applicant, an overview of the pharmacodynamics and pharmacokinetics of the active substances follows:-

Pharmacodynamics

Praziquantel

This active substance is a pyranzinoisoquinoline which causes the spastic paralysis of the musculature some species of cestodes and nematode being more susceptible than others. The action is thought to be due to the depolarising effect on the parasite's cells, causing ensuing damage to the integument and adverse changes to the membrane function.

Pyrantel

This active substance is an imidazothiazole derivative having a broad spectrum of activity against nematodes. There is induction of a neuromuscular blockade via an excitatory effect on nicotinic receptors in the parasite.

Febantel

This active substance is a probenzimidazole with a broad spectrum of activity against nematodes. Activity is via metabolism to fenbendazole and oxfendazole. Ultimately, inhibition of fumarate reductase causes an adverse effect on ATP[2] generation.

Pharmacokinetics

Praziquantel

When administered perorally, praziquantel is absorbed almost entirely from the intestinal tract, following which, the active substance is distributed to all organs. Metabolism reduces praziquantel to inactive forms, which is ultimately secreted

[2] ATP – Adenosine triphoshphate.

in bile. 95% excretion occurs within 24 hours, with only traces of non-metabolised active being excreted. In dog, peak plasma concentration occurs in approximately 2.5 hours.

Pyrantel

After absorption, pyrantel pamoate is almost completely metabolised into inactive metabolites, which are excreted rapidly in the faeces.

Febantel

There is rapid and effective absorption of this active substance, and subsequent metabolisis provides the ensuing anti-anthelmintic activity, via oxfendazole and fenbendazole. These metabolites achieve peak plasma concentrations in approximately 7-9 hours in dogs.

Toxicological Studies

The applicant provided bibliographical data.

- Single Dose Toxicity/ Repeated Dose Toxicity

  No new data were presented to suggest a negative impact on user safety, or that the benefit/risk assessment was any different to that of the reference product.

- Reproductive Toxicity, including teratogenicity, mutagenicity and carcinogenicity

- Data suggesting that febantel is a teratogen at 50 mg/kg bodyweight in rats have meant that section 4.7 of the SPC reflects required statements as cited for the reference product.

Other Studies

There were no reports of immunotoxic or neurotoxic effects caused by the three active substances.

Observations in Humans

The applicant has provided bibliographical data. Praziquantel is used commonly in veterinary medicines, but additionally in human medicine for the treatment of schistosomiasis. A CVMP[3] Summary Report describes the therapeutic dose in man as being from a single dose of 5 – 60 mg/kg bw, to multiple oral doses of 3 x 25 mg/kg bw for up to 3 days to 50 – 60 mg/kg bw for up to 15 days. Pyrantel has been used in human medicine for over 20 years, usually as the embonate

[3] CVMP – Committee for Medicinal Products for Veterinary Use.

salt. Doses are normally 10 – 20 mg/kg bw/day for 1 – 3 days (CVMP Summary Report, Nov 1998). Febantel is not used in human medicine.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which is the same as those of an identical product, Prazitel Plus Tablets for Dogs. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

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 the product will be used mainly by pet owners or veterinarians for use in individual dogs. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13 (3). Bioequivalence was supported by proprietary data and published literature, as bioequivalence was not demonstrable for all relevant substance and metabolites with regard to efficacy.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Praziquantel

This active substance is a pyranzinoisoquinoline which causes the spastic paralysis of the musculature some species of cestodes and nematode being more susceptible than others. The action is thought to be due to the depolarising effect on the parasite's cells, causing ensuing damage to the integument and adverse changes to the membrane function.

Pyrantel

This active substance is an imidazothiazole derivative having a broad spectrum of activity against nematodes. There is induction of a neuromuscular blockade via an excitatory effect on nicotinic receptors in the parasite.

Febantel

This active substance is a probenzimidazole with a broad spectrum of activity against nematodes. Activity is via metabolism to fenbendazole and oxfendazole. Ultimately, inhibition of fumarate reductase causes an adverse effect on ATP[4] generation.

Pharmacokinetics

Praziquantel

When administered perorally, praziquantel is absorbed almost entirely from the intestinal tract, following which, the active substance is distributed to all organs. Metabolism reduces praziquantel to inactive forms, which is ultimately secreted in bile. 95% excretion occurs within 24 hours, with only traces of non-metabolised active being excreted. In dog, peak plasma concentration occurs in approximately 2.5 hours. The active substance is extensively absorbed in dogs, with the main metabolites being hydroxylation products.

Pyrantel

This active substance is poorly soluble in water, causing low absorption in the gut in the target animal. After absorption, pyrantel pamoate is almost completely metabolised into inactive metabolites, which are excreted rapidly in the faeces. Approximately half of eliminated faeces contains unaltered drug.

Febantel

Although this active substance does not appear to have been studies specifically in the dog, there is in most species rapid and effective absorption of this active substance, and subsequent metabolisis provides the ensuing anti-anthelmintic activity, via oxfendazole and fenbendazole. These metabolites achieve peak plasma concentrations in approximately 7-9 hours in dogs.

A supporting proprietary study submitted by the applicant provided some evidence that the three active substances were mutually compatible and effective, although it did not provide evidence of bioequivalence with the reference product.

Tolerance in the Target Species of Animals

The applicant provided bibliographic references describing the target animal's tolerance for each active substance. A pivotal tolerance study was also presented using the product versus the reference product in young dogs. Relevant data suggested that the product was tolerated at no greater risk than that of the reference product.

[4] ATP – Adenosine triphoshphate.

Resistance

It was accepted that no cases of resistance to praziquantel in dogs were seen. In humans, although the active substance is commonly used in some parts of the world, no evidence of resistance has been seen. Some reports of resistance to pyrantel for *T. canis* and *A. Caninum* have been reported, however, this was at a lower dose (5 mg/kg), than that used in the product. No cases of resistance to febantel in dogs have been seen.

IV.B Clinical Studies

Laboratory Trials

An extensive bibliography was presented to support this section of the dossier, providing the results of several published trials which supported the use of the three active substances of Quantilex Plus Tablets for Dogs alone and in combination. Whilst bioequivalence could not be established with the reference product, sufficient data were received in order to draw the conclusion that the product was equally as efficacious as the reference product.

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 product(s) is favourable

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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.

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