

IPAR



Publicly Available Assessment Report for a Veterinary Medicinal Product

Endogard Plus XL Tablets for dogs

PRODUCT SUMMARY

EU Procedure number	IE/V/0539/001-002 (formerly UK/V/0339/001-002)
Name, strength and pharmaceutical form	Endogard Plus XL Tablets for dogs
Active substances(s)	Febantel, Pyrantel embonate, Praziquantel
Applicant	Krka, d.d., Novo mesto Šmarješka cesta 6 8501 Novo mesto Slovenia
Legal basis of application	Generic application (Article 13(1) of Directive No 2001/82/EC)
Target species	Dogs
Indication for use	For the treatment of mixed infestations with the following roundworms and tapeworms in adult dogs and puppies: Nematodes Ascarids: <i>Toxocara canis</i> , <i>Toxascaris leonina</i> (late immature forms and mature forms) Hookworms: <i>Uncinaria stenocephala</i> , <i>Ancylostoma caninum</i> (adults) Cestodes Tapeworms: <i>Taenia</i> spp., <i>Dipylidium caninum</i>
ATCvet code	QP52AC55
Date of completion of the original decentralised procedure	03 June 2011 (IE) 24 November 2010 (UK)
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States	Austria, Belgium, Czech Republic, Denmark, Estonia, Germany, Greece, Hungary, Ireland (now RMS), Italy, Latvia, Lithuania, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, UK added as CMS

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for

approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

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

Endogard Plus Flavour Tablets for Dogs and Endogard Plus XL Tablets for Dogs are intended for the treatment of mixed infestations with roundworms and tapeworms in dogs. Endogard 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. Endogard 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 products are produced and controlled using validated methods and tests which ensure the consistency of the products released on the market. It has been shown that the products can be safely used in the target species, the slight reactions observed are indicated in the SPC. The products are 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 products was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

Endogard Plus Flavour Tablets for Dogs contain 50 mg praziquantel, 144 mg pyrantel embonate and 150 mg febantel per tablet. Endogard 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. Endogard 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. Endogard Plus Flavour Tablets for Dogs are available in 4, 10, 30, 50, 100 or 300 tablets. Endogard Plus XL Tablets for Dogs are available in 2, 4, 10, 12, 24, 30, 50, 60, 100 or 102 tablets.

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 at a licensed manufacturing site.

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 specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with the specifications 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.

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.

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.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

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 by 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 first phase 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

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 Ca²⁺ channels in the gut lumen of parasites, causing an influx of Ca²⁺ 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 Endogard 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 *Ancylostoma caninum* and *Uncinariastenocephalus*, (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 Endogard Plus Flavour Tablets and Drontal Plus Flavour Tablets to Endogard 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.