IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Exitel Plus Tablets for Dogs

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PRODUCT SUMMARY

EU Procedure number	IE/V/0242/001/MR
Name, strength and pharmaceutical form	Exitel Plus Tablets for Dogs
Active substance(s)	Praziquantel Pyrantel embonate Febantel
Applicant	Chanelle Pharmaceuticals Manufacturing Ltd. Loughrea Co. Galway Ireland
Legal basis of application	Hybrid application in accordance with Article 13.3 of Directive 2001/82/EC as amended.
Date of Authorisation	27/10/2009
Target species	Dogs
Indication for use	Control of gastrointestinal tapeworms and roundworms of dogs
ATCvet code	QP52AA51
Concerned Member States	UK, DE, BE, ES, NL, AT, EL, IT, FI, SE, DK, CY, EE, PT, LU, PL, CZ, LV, LT, NO, HU, IS, SK, BG, RO, SI

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

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.
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.

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II QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains the following active substances: praziquantel (50.0 mg/tablet), pyrantel embonate (144.0 mg/tablet) and febantel (150.0 mg/tablet) and the excipients microcrystalline cellulose, lactose monohydrate, sodium laurilsulfate, magnesium stearate, croscarmellose sodium and colloidal anhydrous silica.

The product is packaged in polythene / aluminium foil strips (30 µm / 30 gsm extruded polythene) or in blister packs made of a 45 µm soft temper aluminium foil and a 25 µm hard temper aluminium foil. The packaging materials comply with relevant EU standards.

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.

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. Each is an established substance described in the European Pharmacopoeia. 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.

Other substances in the product comply with European Pharmacopoeia specifications.

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

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 on intermediate products

Not applicable.

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 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 substances when stored under the approved conditions.

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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

Not applicable

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Exitel Plus has been formulated to have the same qualitative and quantitative composition, in terms of active substances, as the authorised reference product, Drontal Plus. Given that bioequivalence could not be demonstrated through bioavailability studies, the present application has been submitted in accordance with Article 13(3) of the Directive, as amended (so called 'hybrid' application) and safety and efficacy are supported by proprietary data and published literature.

An extensive bibliography has been provided which adequately characterises the toxicological properties of each active substance. Based on available toxicity data, it is evident that the three active substances have low toxic potential.

A satisfactory user safety assessment was provided. It is concluded that the product is not a risk to the user; however, a precautionary statement to wash hands after use is included on the product literature. Further, given the nature of this application (hybrid (generic) application), the fact that Exitel Plus has been formulated to have the same composition, in terms of active substances, as the

authorised reference product, Drontal Plus,

that all excipients in the formulation are commonly used in the manufacture of tablets for animal and human use and are generally regarded as safe, and

the fact that the proposed conditions of use of Exitel Plus are identical to those of the reference product,

it can be assumed that Exitel Plus does not present any greater risk to the user relative to that posed by the reference product, Drontal Plus. The user safety statements proposed for Exitel Plus are in line with those that appear on the authorised SPC of the reference product.

It is accepted that this product does not pose a risk to the environment when used in accordance with label recommendations.

IV CLINICAL ASSESSMENT (EFFICACY)

Exitel Plus has been formulated to have the same qualitative and quantitative composition, in terms of active substances, as the authorised reference product, Drontal Plus. Given that bioequivalence could not be demonstrated through bioavailability studies, the present application has been submitted in accordance with Article 13(3) of the Directive, as amended (so called 'hybrid' application) and safety and efficacy are supported by proprietary data and published literature.

An extensive bibliography has been provided which adequately characterises the pharmacological properties of each component. Given the nature of this application (hybrid (generic) application, based on the authorised reference product, Drontal Plus), it can be assumed that the pharmacodynamic effects of the individual actives will not be adversely altered by administration with others in the combination. Further, it can be assumed that the pharmacokinetic properties of each of the individual actives following administration to dogs as the combination tablet, Exitel Plus, will be similar to pharmacokinetic properties of each of the individual actives following administration to dogs as the combination tablet, Drontal Plus.

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While it is not possible to conclude that the test and reference products are bioequivalent based on the findings of a comparative pharmacokinetic study conducted in dogs, it is 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 febantel, fenbendazole and oxfendazole,
- Pyrantel is poorly soluble in water leading to low absorption from the gastrointestinal tract, with a high proportion of the administered dose remaining in the GIT to act 'locally'. Therefore, use of plasma PK data to conclude on efficacy of the pyrantel component of the product may not be appropriate

In terms of efficacy, the available data suggest that the test product is likely to be at least as effective as the authorised reference product.

In addition to the *in vivo* study, the Applicant has provided comparative data where the dissolution profiles of the test and reference products were investigated *in vitro*. Based on the data presented, the dissolution profile for the test and reference products is comparable: For each of the active substances, greater than 80% dissolution was achieved within 15-20 minutes. Given the similarity in formulation (in terms of active substances) and the comparable dissolution profiles, differences between the test and reference products with respect to efficacy are not to be expected.

Given the nature of the application (that is, a hybrid (generic) application) the proposed indications and the proposed doses for the individual active substances reflect those of the authorised reference product. In addition, extensive bibliography has been presented 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 in the combination are justified. Further, administration of the combination can be expected to be efficacious against the claimed target parasites.

In relation to target animal safety, it is evident, based on available toxicity data, that the three active substances are very well tolerated when administered individually. As the modes of action of each of the actives are different, a wide safety margin is also expected for the combination. Available bibliographic data indicate that the reference product is well tolerated in the target species. In addition, the Applicant has conducted a target animal safety study confirming that Exitel Plus is well tolerated when administered to pups at doses up to five times the recommended treatment dose or when administered at the recommended treatment dose for up to three days. Adverse effects following administration of the recommended treatment dose on a single occasion are not expected. Further, given the fact that Exitel Plus has been formulated to have the same composition, in terms of active substances, as the

- authorised reference product, Drontal Plus,
- that all excipients in the formulation are commonly used in the manufacture of tablets for animal and human use and are generally regarded as safe
- In vitro dissolution profiles for the test and reference products are comparable, indicating similar rate of release of active substances following ingestion, and
- the fact that the proposed conditions of use of Exitel Plus are identical to those of the reference product,

it can be assumed that Exitel Plus is unlikely to present any greater risk to the target animal relative to that posed by the reference product, Drontal Plus. The information included in sections 4.6 and 4.10 of the SPC proposed for Exitel Plus is in line with the information that appears on the authorised SPC of the reference product and can be accepted.

In relation to resistance, the available data suggest that the active substances included in Exitel Plus continue to be effective against target canine pathogens with limited reports of resistance. Further, given the fact that Exitel Plus has been formulated to have the same composition, in terms of active substances, as the

- authorised reference product, Drontal Plus,

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the fact that the proposed conditions of use of Exitel Plus are identical to those of the reference product,
it can be assumed that Exitel Plus is unlikely to present any greater risk for resistance emergence than that posed by the reference product, Drontal Plus.

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.

VI 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.

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**.**

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