Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Cardisan 1.25 mg Chewable Tablets for Dogs
Cardisan 2.5 mg Chewable Tablets for Dogs
Cardisan 5 mg Chewable Tablets for Dogs
Cardisan 10 mg Chewable Tablets for Dogs
Cardisan 15 mg Chewable Tablets for Dogs

Date Created: January 2023

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Cardisan 1.25 mg Chewable Tablets for Dogs Cardisan 2.5 mg Chewable Tablets for Dogs Cardisan 5 mg Chewable Tablets for Dogs Cardisan 10 mg Chewable Tablets for Dogs Cardisan 15 mg Chewable Tablets for Dogs
Applicant	Alfasan Nederland B.V., Kuipersweg 9, 3449 JA Woerden, 3449, The Netherlands
Active substance	Pimobendan
ATC Vetcode	QC01CE90
Target species	Dogs
Indication for use	For the treatment of canine congestive heart failure originating from dilated cardiomyopathy or valvular insufficiency (mitral and/or tricuspid valve regurgitation).

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	The application for the 2.5 mg tablet is for an MA submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended by 2004/28/EC (generic application). The applications for the four remaining tablet strengths are for MAs submitted in accordance with Article 13(3) of the same Directive (generic 'hybrid' applications).
Date of conclusion of the procedure	13/12/2022

I. SCIENTIFIC OVERVIEW

These products are chewable tablets and contain 1.25 mg, 2.5 mg, 5 mg, 10 mg or 15 mg of pimobendan. The proposed indications are for the treatment of canine congestive heart failure originating from dilated cardiomyopathy or valvular insufficiency (mitral and/or tricuspid valve regurgitation) in dogs. The proposed dosage is 0.2 - 0.6 mg/kg (ideally 0.5 mg/kg) divided into two daily doses, given orally. In case of congestive heart failure, life-long treatment is recommended.

The application for the 2.5 mg tablet is for an MA submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended by 2004/28/EC (Generic application). The applications for the four remaining tablet strengths (1.25, 5, 10 and 15mg) are for MAs submitted in accordance with Article 13(3) of the same Directive (generic 'hybrid' applications). The reference product for all five strengths of the proposed product is Vetmedin 2.5 mg Hard Capsules, marketed by Boehringer Ingelheim Animal Health UK Ltd, first authorised in the UK on 21 July 1999. The marketing authorisation for this product expired in the UK on 21 May 2013. The four generic hybrid applications submitted in accordance with Article 13(3) are done so because the relevant proposed products are of different strengths to the reference product.

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

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 1.25mg, 2.5mg, 5mg, 10mg or 15mg of pimobendan and the excipients citric acid, povidone, lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, chicken flavour, yeast (dried), silica colloidal hydrated and magnesium stearate.

The container/closure system consists of aluminium-OPA/aluminium/PVC blister strips containing 10 tablets (1.25 mg, 2.5 mg, 5 mg and 10 mg) or 5 tablets (15 mg). These blister strips will then be packaged within cardboard boxes containing 30, 60, 90, 100 or 120 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 a licensed manufacturing site. The manufacturing process consists of the production of a granulate including wet granulation, drying and milling. Then production of the final powder blend and tablets before being packaged.

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

II.C. Control of Starting Materials

The active substance is pimobendan an established active substance 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. Appropriate Certificates of Suitability provided.

All of the excipients, except for yeast (dried) and chicken flavour, are described in the Ph. Eur. and are supplied in accordance with their monographs. Both

yeast (dried) and chicken flavour are known excipients in tablets for dogs and the specifications provided are acceptable.

Satisfactory information on the packaging materials of the bulk product and tablets have been provided.

II.C.4. Substances of Biological Origin

Scientific data and certificates of suitability issued by the EDQM have been provided and 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.

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 characters, tablet diameter, average mass, resistance to crushing, uniformity of dosage units, identification of pimobendane, assay of pimobendane, pimobendan related substances, dissolution of pimobendane and microbiological quality.

II.F. Stability

Stability data on the active substance has been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 5 years

This veterinary medicinal product does not require any special storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Due to the legal basis of the application, no new pharmacological or toxicological studies have been submitted except for bioequivalence. User risk assessments (URA) and environmental risk assessments (ERA) in accordance with current guidance were provided.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that users are identified as dog owners, including children. Dermal contact (including hand-to-mouth) was considered as the main route of exposure during the subdivision and administration of the tablets. Accidental ingestion by a child is also considered.

The user safety information in the SPC is similar to that authorised for the reference product and is identical to that authorised for a comparable product containing the same active substance.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following user recommendations are appropriate:

- This product may cause tachycardia, orthostatic hypotension, flushing of the face and headaches.
- To avoid accidental ingestion, especially by a child, unused tablet parts should be placed back into the blister and carton and carefully kept away from children.
- Part used tablets should be used at the time of the next dose.
- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
- Wash hands after use.

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.

Use of the product will not impact environmental safety when the product is used as recommended.

IV. CLINICAL DOCUMENTATION

Pharmacology

As these are generic/hybrid applications submitted according to Part 2 of Schedule 1 (Marketing Authorisations) Paragraph 10 of the Veterinary Medicines Regulation and according to Article 13(1)/Article 13(3) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been established, documentation on safety and efficacy is not required. No additional data in relation to pharmacodynamics and pharmacokinetics has been provided.

Tolerance in the Target Species

The applicant has claimed that as these are generic/hybrid applications submitted according to Part 2 of Schedule 1 (Marketing Authorisations) Paragraph 10 of the Veterinary Medicines Regulation and according to Article 13(1)/Article 13(3) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been established, documentation on safety and efficacy is not required. The applicant has therefore not provided additional data from standalone target animal safety studies.

IV.II. Clinical Documentation

The applicant has submitted two well-conducted, GLP-compliant, single dose, two-period, two sequence, randomised, cross-over studies for the demonstration of plasma level bioequivalence between the test and reference products for the active substance, pimobendan in dogs.

The first of these studies was conducted using Vetmedin 5 mg chewable tablets as the reference product but ultimately failed to demonstrate bioequivalence. The second study instead used Vetmedin 2.5 mg hard capsules as the reference product and the applicant has claimed bioequivalence was demonstrated by this pivotal study. The German-authorised Vetmedin 2,5 mg Kapseln für Hunde used as the reference product in the second bioequivalence study, is considered to be sufficiently identical to the UK-authorised Vetmedin 2.5 mg hard capsules used as the reference product in the current applications. The administered dose was in accordance with their respective SPCs. The level of pimobendan in canine plasma was determined using a validated liquid chromatography mass spectrometry bioanalytical method.

The applicant pre-defined that bioequivalence may be concluded if the 90% confidence intervals for the ratio of the means for AUC[3] is within 80 - 125% and for C_{max}[4] within 70 - 143%. The justification given for using the broader interval

[3] AUC – Area under the dosing curve.
[4] Cmax – maximum concentration of active substance in blood plasma.

for the latter was this is a twice daily lifelong medication and clinical efficacy is therefore more reliant on bioequivalence of AUC. The applicant has used the results of the two bioequivalence studies to demonstrate that the C_{max} data for the candidate product lay between that of the clinically interchangeable Vetmedin capsules and Vetmedin tablets. Both Vetmedin products have been marketed for over 20 years and are both considered safe and efficacious. Therefore, it is safe to assume the wider limit for C_{max} would pose any risk to target animal safety and/or efficacy for the proposed indications.
The results of the pivotal second bioequivalence study indicate that the 90% confidence interval for the test and reference mean ratio of AUC (85 - 99%) lies within the standard acceptance limits of 80 - 125% presented. The 90% confidence interval for C_{max} (75 - 96%) lies within the pre-defined broader limits of 70 - 143%. Therefore, the plasma level bioequivalence of pimobendan between the test and reference products is considered to have been sufficiently demonstrated.

Regarding the four additional strengths of the candidate products, the applicant presented sufficient *in vitro* dissolution data to justify why bioequivalence only needed to be demonstrated for the 2.5 mg formulation.

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.

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.

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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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