College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Cardisure Flavoured 1.25 mg Tablets for Dogs (AU, BE, DE, GR, IE, IT, LU, NL, PL, PT, ES, UK)
Cardisure flavoured vet. 1.25 mg Tablets for Dogs (DK)
Cardisure vet. 1.25 mg Tablets for Dogs (FI, SE, NO)
Cardisure 1.25 mg Tablets for Dogs (FR)

Cardisure Flavoured 2.5 mg Tablets for Dogs (AU, BE, DE, GR, IE, IT, LU, NL, PL, PT, ES, UK)
Cardisure flavoured vet. 2.5 mg Tablets for Dogs (DK)
Cardisure vet. 2.5 mg Tablets for Dogs (FI, SE, NO)
Cardisure 2.5 mg Tablets for Dogs (FR)

Cardisure Flavoured 5.0 mg Tablets for Dogs (AU, BE, DE, GR, IE, IT, LU, NL, PL, PT, ES, UK)
Cardisure flavoured vet. 5.0 mg Tablets for Dogs (DK)
Cardisure vet. 5.0 mg Tablets for Dogs(FI, SE, NO)
Cardisure 5.0 mg Tablets for Dogs (FR)

Cardisure Flavoured 10 mg Tablets for Dogs (AU, BE, DE, GR, IE, IT, LU, NL, PL, PT, ES, UK)
Cardisure flavoured vet. 10 mg Tablets for Dogs (DK)
Cardisure vet. 10 mg Tablets for Dogs(FI, SE, NO)
Cardisure 10 mg Tablets for Dogs (FR)

Date Updated: August 2021

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0280/001/DC NL/V/0280/002/DC NL/V/0280/003/DC NL/V/0280/004/DC
Name, strength and pharmaceutical form	Cardisure Flavoured 1.25 mg Tablets for Dogs Cardisure Flavoured 2.5 mg Tablets for Dogs Cardisure Flavoured 5.0 mg Tablets for Cardisure Flavoured 10 mg Tablets for Dogs
Applicant	Dechra Regulatory BV Handelsweg 25, 5531 AE Bladel The Netherlands
Active substance	Pimobenden
ATC Vetcode	QC01E90
Target species	Dogs
Indication for use	For the treatment of canine congestive heart failure originating from valvular insufficiency (mitral and/or tricuspid regurgitation) or dilated cardiomyopathy.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	The applications for Cardisure 1.25 mg and 5 mg Flavoured Tablets are generic applications submitted in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC. The applications for Cardisure 2.5 mg and 10 mg Flavoured Tablets are 'generic hybrid' applications submitted in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	20th April 2011.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Norway, Poland, Portugal, Spain, Sweden.

I. SCIENTIFIC OVERVIEW

The applications for Cardisure 1.25 mg and 5 mg Flavoured Tablets are generic applications submitted in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC. The applications for Cardisure 2.5 mg and 10 mg Flavoured Tablets are 'generic hybrid' applications submitted in accordance with Article 13 (3) of Directive 2001/82/EC as amended. These products are light brown round tablets, scored on one side and plain on the other side. The tablets can be divided into 4 equal parts, apart from the 1.25 mg presentation, which may be divided into 2 equal parts. The tablets are for the treatment of canine congestive heart failure, originating from valvular insufficiency (mitral and/or tricuspid regurgitation), or dilated cardiomyopathy. The tablets are available as 1.25 mg, 2.5 mg, 5 mg and 10 mg flavoured tablets, and should be administered on an empty stomach, at least one hour before meals. The preferable daily dose is 0.5 mg pimobendan per kg bodyweight, with the range of dose being given as from 0.2 mg to 0.6 mg pimobendan per kg bodyweight per day. The dose should be given in two administrations, (0.25 mg/kg bodyweight each), one half dose in the morning, and the other approximately 12 hours later. The maintenance dose should be adjusted by the veterinarian, according to the severity of disease.

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.

The reference products are Vetmedin 2.5 mg Hard Capsules, Vetmedin 5 mg Flavour Tablets and Vetmedin 5 mg Flavour Tablets, sourced from The Netherlands, and used in a bioequivalence study.

II. QUALITY ASPECTS

A. Composition

The product contains pimobendan and excipients cellulose, microcrystalline (E460) croscarmellose sodium, magnesium stearate and natural meat flavour.

For the 5 mg and 10 mg per tablet packs, the container system is an aluminium/PVC/PE/PVDC blister pack, consisting of 10 tablets per blister and 2, 5, 10 or 25 blisters per carton, or 5 tablets per aluminium-aluminium blister, consisting of 4, 10, 20 or 50 blisters per carton. For the 1.25 mg and 2.5 mg tablet packs, the container system is an aluminium/PVC/PE/PVDC blister pack, consisting of 10 tablets per blister and 2, 5, 10 or 25 blisters per carton, or 10 tablets per aluminium-aluminium blister, consisting of 2, 5, 10 or 25 blisters per carton. The particulars of the containers and controls performed are provided and conform to the regulation. The absence of preservative was 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.

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.

Excipients complying with the Ph. Eur. are microcrystalline cellulose, croscarmellose sodium and magnesium stearate. The natural meat flavour complies with the European Flavouring Directive 88/338/EEC.

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

A declaration was received from the applicant stating that the finished product is in compliance with the latest version of the CPMP[1]/CVMP[2] guideline on transmissible spongiform encephalopathies (EMEA/410/01 Rev. 2 of October 2003). A UK Format 3 state was also supplied, confirming that the active substance and excipients are sourced from non-animal origins.

E. Control on intermediate products

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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. Analyses include appearance, average mass, uniformity of mass, uniformity of dosage units friability, resistance to crushing, dissolution, microbial quality, and identity and assay of pimobendan.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Stability studies were conducted on batches of 1.25 mg product and batches of 10 mg product. The tablets were stored under VICH[3] conditions. Additional stability data were

[1] CPMP – The Committee for Proprietary Medicinal Products.
[2] CVMP – The Committee for Medicinal Products for Veterinary Use.
[3] VICH - International Cooperation on harmonisation of Technical Requirements for Registration of Veterinary Products.

provided for pilot batches of all tablet strengths. Satisfactory results were demonstrated over the relevant time periods. Implications with regard to the storage of the product in the blister packs prompted the addition to the SPC of the temperature storage precaution 'Do not store above 30ºC.'

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 30 months.
Shelf life of divided tablets after first opening the blister: 3 days.
Return any divided tablet to the opened blister and use within 3 days.
Do not store above 30°C.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As these were generic applications according to Article 13, and bioequivalence with a reference product has been demonstrated, results of pharmacological and toxicological tests were not required.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and the environment.

III.A Safety Testing

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline which shows that warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:-

- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
- Wash hands after use.
- Advice to doctors: accidental ingestion, especially by a child, may lead to the occurrence of tachycardia, orthostatic hypotension, flushing of the face and headaches.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. 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)

IV.A Pre-Clinical Studies

Pharmacology

A three-way crossover, GLP[4]-compliant bioequivalence study was submitted comparing three pimobendan-containing formulations. The test product was a 2.5 mg pimobenden-containing tablet, with reference products Vetmedin 2.5 mg Hard Capsules and Vetmedin 5 mg Flavour Tablets. A suitable number of dogs were acclimatised before division into three groups, each of which was treated with the three products, with a wash-out period in between treatments of 7 days. Biological and physiological parameters were examined at various time-points throughout the trial. Suitable results showed that Vetmedin 5 mg Flavour Tablets and the test product were bioequivalent for AUC_t[5] and C_{max}[6]. Dissolution studies were performed in order to extrapolate data to the other strengths of the product.

Tolerance in the Target Species of Animals

No data were required for this section, as the products were authorised under Article 13 of Directive 2001/82/EC, as amended.

IV.B Clinical Studies

No data were required for this section, as the products were authorised under Article 13 of Directive 2001/82/EC, as amended.

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.

[4] GLP - Good Laboratory Practise.
[5] AUC_t – Total area under the concentration versus time profile to last sampling time.
[6] C_{max} – Maximum concentration of a medicinal product.

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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

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.

•	19 June 2020	Marketing Authorisation Holder change
•	30 August 2018	Change in RMS from UK to NL.
•	12 July 2016	Renewal – UK as RMS
•	24 June 2015	Change in name of supplier of a starting material. Tightening of specification limits of the active substance. Addition of a new specification parameter for the active substance.
•	17 June 2015	Changes to the labelling and package leaflet.
•	07 August 2014	To add an additional supplier of the starting material used in the manufacturing process of the active substance.
•	13 February 2014	Addition of a new manufacturing site responsible for the finished product, primary packaging, secondary packaging, batch control testing and batch release.
•	24 October 2013	Addition of a manufacturer for a starting material and changes in the manufacturing process of the active substance.
•	11 July 2013	Variation to correct the specification limits for protein of an excipient due to a typing error in

		original submission.
•	25 March 2013	Change of QPPV and contact details for the QPPV of an existing pharmacovigilance system.
•	20 December 2012	Minor change in the manufacturing process of the active substance.
•	18 October 2012	Minor change to an approved test procedure used in the manufacturing process of the active substance.
•	04 April 2012	Change in batch size of the active substance.
•	04 August 2011	Change to batch release arrangements and quality control testing of the finished product.