Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Pimocard 1.25 mg Flavoured Tablets for Dogs
Pimocard 2.5 mg Flavoured Tablets for Dogs
Pimocard 5 mg Flavoured Tablets for Dogs
Pimocard 10 mg Flavoured Tablets for Dogs
(Belgium, Estonia, Germany, Ireland, Italy, Lithuania, The Netherlands, United Kingdom)

Cardisure 1.25 mg Flavoured Tablets for Dogs
Cardisure 2.5 mg Flavoured Tablets for Dogs
Cardisure 5 mg Flavoured Tablets for Dogs
Cardisure 10 mg Flavoured Tablets for Dogs
(Bulgaria, Croatia, Czech Republic, Hungary, Romania, Slovakia and Slovenia only)

Pimosure 1.25 mg Flavoured Tablets for Dogs
Pimosure 2.5 mg Flavoured Tablets for Dogs
Pimosure 5 mg Flavoured Tablets for Dogs
Pimosure 10 mg Flavoured Tablets for Dogs
(Portugal)

Pimosure sabor 1.25 mg tablets for dogs
Pimosure sabor 2.5 mg tablets for dogs
Pimosure sabor 5 mg tablets for dogs
Pimosure sabor 10 mg tablets for dogs
(Spain)

Date Created: April 2016

PuAR correct as of 30/08/2018 when RMS was transferred to NL.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0580/001-4/MR
Name, strength and pharmaceutical form	Pimocard 1.25 mg Flavoured Tablets for Dogs Pimocard 2.5 mg Flavoured Tablets for Dogs Pimocard 5 mg Flavoured Tablets for Dogs Pimocard 10 mg Flavoured Tablets for Dogs
Applicant	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel The Netherlands
Active substance(s)	Pimobendan
ATC Vetcode	QC01CE90
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 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 application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	21 October 2015
Date product first authorised in the Reference Member State (MRP only)	15 June 2012
Concerned Member States for original procedure	First Use Belgium, Czech Republic, Estonia, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Portugal, Slovakia, Slovenia, Spain. Repeat Use Bulgaria, Croatia, Cyprus, Romania.

I. SCIENTIFIC OVERVIEW

Pimocard 1.25 mg and 5 mg Flavoured Tablets have been developed as generics products whilst Pimocard 2.5 mg and 10 mg Flavoured Tablets have been developed as generic hybrids. The reference products are Vetmedin 2.5 mg Hard Capsules, Vetmedin 5 mg Flavour Tablets authorised in the UK in 1999 and 2007 respectively, and Vetmedin 5 mg Flavour Tablets sourced from The Netherlands. Bioequivalence has been shown through *in vivo* comparison of the 2.5 mg tablet with the reference product, and by extension, has been demonstrated through suitable dissolution studies for the remaining strengths.

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 tablets are for the treatment of canine congestive heart failure, originating from valvular insufficiency (mitral and/or tricuspid regurgitation), or dilated cardiomyopathy. The products are contraindicated in hypertrophic cardiomyopathies or in diseases in which an improvement in cardiac output cannot be achieved for functional or anatomical reasons (e.g. aortic stenosis). In addition, it should not be used in dogs with severe impairment of liver as pimobendan is mainly metabolised by the liver.

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, 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 according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

II.A. Composition

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

For the 1.25 mg and 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. 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. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of formulation and 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.

II.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. The manufacturing method is a standardised compression of tablets. 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.). Data on the active substance were supplied in an Active Substance Master File (ASMF). 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.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

Excipients described in the Ph. Eur. are microcrystalline cellulose, croscarmellose sodium and magnesium stearate. They are manufactured in accordance with their respective monographs. The natural meat flavour complies

with the European Flavouring Directive 88/338/EEC. Certificates of analysis have been supplied.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

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. Control tests on the finished product include those for identification and assay of the active substance, appearance, average mass, friability, resistance to crushing, dissolution and microbial quality.

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.

II.F. 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. A retest period of 30 months is supported.

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. Data were provided for batches of the 1.25 mg and 10 mg tablets stored at 25°C/60% RH for up to 30 months, at 30°C/65% RH for 12 months, at 40°C/75% RH for 6 months and at 5°C for 6 months.

In-use stability studies were also performed. Data were provided for 1.25 mg and 10 mg tablets following division and unprotected storage on a glass tray at 25°C/60% RH for 72 hours.

G. Other Information

Shelf life of the finished product as packaged for sale: 30 months.

Shelf life of divided tablets after first opening the blister: Remaining tablets should be given at the next administration.
Do not store above 30°C.
Return any divided tablet to the opened blister.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

As these were generic and generic hybrid applications according to Article 13 (1) and 13 (3) respectively, and bioequivalence with a reference product has been demonstrated, results of pharmacological tests were not required.

Toxicological Studies

As these were generic and generic hybrid applications according to Article 13 (1) and 13 (3) respectively, and bioequivalence with a reference product has been demonstrated, results of toxicological tests were not required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that identifies pet owners as the most likely to be exposed to the product. The main routes of exposure have been identified as dermal, during administration, or accidental ingestion by a child. 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.

Environmental Safety

An Environmental Risk Assessment (ERA) has been submitted. The ERA was conducted in accordance with VICH and CVMP guidelines.

Phase I:
The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The product will only be used to treat individual dogs and as a result environmental exposure will be low. As the product is only intended to treat non-food animals a Phase II ERA was not 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 DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics
As these were generic and generic hybrid applications according to Article 13 (1) and 13 (3) respectively, and bioequivalence with a reference product has been demonstrated, results of pharmacodynamics data were not required.

Pharmacokinetics
An *in vivo* bioequivalence study was provided for Pimocard 2.5 mg tablets in support of the generic application. In addition, *in vitro* dissolution data were provided for the remaining homothetic strengths for comparison. Further bioequivalence studies were not required.

Bioequivalence Study
A three-way crossover, GLP[3]-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. Each dog received 2.5 mg of pimobendan, 0.1-0.3 mg/kg, which corresponded to one 2.5 mg tablet or half a 5 mg tablet. Doses were administered following overnight fasting.

Biological and physiological parameters were examined at various time-points throughout the trial. Blood samples were collected for analysis before treatment and at regular intervals up to 8 hours post-treatment. Pivotal pharmacokinetic parameters, AUC[4] and C_{max}[5], were determined from the blood plasma and the 90% confidence intervals (CI) were calculated. The predefined acceptance criteria for the 90% CI were 80-125% for AUC and 70-143% for C_{max}.

The results show a similar pharmacokinetic profile for both products. The 90% CI were calculated for both parameters for the test product compared with each reference product. The 90% CI fell within the predefined acceptance limits for both parameters for the test product compared to the 5 mg reference product and suitable in-depth analysis also determined bioequivalence for the 2.5 mg product. Bioequivalence with the reference product was accepted.

[3] GLP - Good Laboratory Practise.
[4] AUC – Area under the curve
[5] C_{max} – Maximum plasma concentration

Dissolution Study

A comparative dissolution study has been submitted to compare the dissolution profiles of the 4 different tablet strengths to determine their *in vitro* equivalence. The dissolution studies were conducted using 3 different dissolution media, at 3

3 different pH values (pH 2.2, 4.5 and 6.8). Samples were collected at regular intervals from 5 to 60 minute and pimobendan content in the dissolution media was determined.

The results showed similar dissolution profiles for the 4 dosage strengths in each media. *In vitro* equivalence of all strengths has been satisfactorily demonstrated, therefore bioequivalence, as shown between the reference product and 2.5 mg tablets, can be extrapolated to the remaining tablet strengths.

Tolerance in the Target Species

As these were generic and generic hybrid applications according to Article 13 (1) and 13 (3) respectively, and bioequivalence with a reference product has been demonstrated, results of tolerance studies were not required.

IV.II. Clinical Documentation

As these were generic and generic hybrid applications according to Article 13 (1) and 13 (3) respectively, and bioequivalence with a reference product has been demonstrated, results of clinical trials were not required.

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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