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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Pimovita 1.25 mg chewable tablets for dogs
Pimovita 2.5 mg chewable tablets for dogs
Pimovita 5.0 mg chewable tablets for dogs
Pimovita 10 mg chewable tablets for dogs

MODULE 1

PRODUCT SUMMARY

EU Procedure number	HU/V/0122/001-004/MR
Name, strength and pharmaceutical form	Pimovita 1.25 mg chewable tablets for dogs Pimovita 2.5 mg chewable tablets for dogs Pimovita 5 mg chewable tablets for dogs Pimovita 10 mg chewable tablets for dogs
Applicant	ZYLAVET Pharmaceuticals Ltd. 2143 Kistarcsa, Batthyány u. 6. Hungary
Active substance(s)	pimobendan
ATC Vetcode	QC01CE90
Target species	dog
Indication for use	For the treatment of canine congestive heart failure originating from dilated cardiomyopathy or valvular insufficiency (mitral and/or tricuspid valve regurgitation). For the treatment of dilated cardiomyopathy in the preclinical stage (asymptomatic with an increase in left ventricular end-systolic and end-diastolic diameter) in Doberman Pinschers following echocardiographic diagnosis of cardiac disease.

Product name	Application number
Applicant	MRP/DCP
	Publicly available assessment report

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	HU/V/0122/001-004/MR application in accordance with Article 13 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	25/02/2015
Date product first authorised in the Reference Member State (MRP only)	18/10/2014
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Iceland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom

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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product (one chewable tablet) contains 250 mg pimobendan as active substance, and the excipients (lactose monohydrate, microcrystalline cellulose, pregelatinised starch, sodium starch glycolate (Type A), Macrogol 6000, stearoyl macrogoglycerides, dried yeast, liver powder flavour, talc andmagnesium stearate).

The container/closure system is heat sealed Polyamide/Aluminium/PVC blister strip containing 10 tablets.

The choice of the formulation is 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 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 substance is pimobendan, an established active substance described in the No. 2179 monograph European Pharmacopoeia. 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.

Scientific data and certificates of analysis 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.

D. Control on intermediate products

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

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.

F. Stability

Lack of stability data on the active substance have been justified having regard to the provided CEP of the active substance manufacturer.

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

Process validation report, analytical validation reports, CEP of the active substance.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of safety and residue tests are not required.

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics
Since the application was made in accordance with Article 13(a) of Directive 2001/82/EC, for Pimovita as a generic of the reference product, Vetmedin, submission of data on pharmacodynamics are not required.

Pharmacokinetics
Since the application was made in accordance with Article 13(a) of Directive 2001/82/EC, for Pimovita as a generic of the reference product, Vetmedin, submission of data on pharmacokinetics are not required.
Essential similarity of Pimovita and Vetmedin chewable tablets has been demonstrated after the evaluation of in vivo and in vitro dissolution data.

Toxicological Studies
Since the application was made in accordance with Article 13(a) of Directive 2001/82/EC, as a generic application, the submission of the results of toxicological tests are not required because the toxicological characteristics of the test and the reference product are the same.

Observations in Humans

Pimobendan was used for the treatment of human heart failures, after its effect was discovered in 1990. It is a class III. phosphodiesterase inhibitor, a benzimidazole derivative. It was extensively tested for the treatment of moderate and severe heart failure (Rector and Cohn, 1992.) It was only registered in Japan, because some symptoms appeared to be sustained in patients receiving pimobendan. Milrinone and amrinone in the same class III inhibitor family proved to be more efficacious than pimobendan.

Pimobendan has a positive inotropic effect, vascular and airway dilation and inhibition of platelet aggregation. (In: Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition 1996.) See below: 3.A.5. User safety

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the potential risk to the user posed by Pimovita 1.25 mg, 2.5 mg, 5 mg and 10 mg Chewable Tablets will not be any greater than that posed by the reference product.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

Phase I

The environmental risk assessment can stop in Phase I because Pimovita 1.25 mg, 2.5 mg, 5 mg and 10 mg chewable Tablets are recommended for individual treatment of non-food animals,

Conclusion

Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residue Testing

As the product of Pimovita 1.25 mg, 2.5 mg, 5 mg and 10 mg chewable tablets are only used for treatment of dogs (i.e. non-food producing animals), this part of the safety documentation is not relevant.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.
The in vivo bioequivalence of the 5 mg strength of Pimovita with the concerning 5 mg strength of Vetmedin as reference product has been demonstrated in dogs while in vitro bioequivalence data were presented for additional strengths.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The application is submitted in accordance with Article 13 of Directive 2001/82/EC. For a generic veterinary medicinal product, pharmacodynamic data are not required as they have already been presented for the reference product.

Pharmacokinetics

The application is submitted in accordance with Article 13 of Directive 2001/82/EC. For a generic veterinary medicinal product, information on pharmacokinetics is not required as it has already been presented for the reference product.

Tolerance in the Target Species of Animals

Being a generic application, target species tolerance studies are not required as they have already been presented for the reference product.

IV.B Clinical Studies

Laboratory Trials

The applicant has conducted in vitro bioequivalence (dissolution) studies which show similarity to those of the reference product.

Field Trials

The applicant has conducted a GLP cross-over bioequivalence study in dogs following a single oral administration of Vetmedin 5 mg Chewable Tablets (reference item) and Pimovita 5 mg Chewable Tablets (test item). Based on the results obtained from the study, the test item and the reference item were found bioequivalent in dogs, since the 90% confidence interval for the ratio of the two treatment means of C_{max} and AUC_t were entirely contained within the specified limits 80% to 125% for both pimobendan (parent compound) and its active, demethylated metabolite, respectively.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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 Vetrinary 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.

Quality changes

Summary of change (Application number)	**Section updated in Module 3**	**Approval date**
Change in the name of the medicinal product HU/V/0122/1-4/IB/001/G	N/A	16.10.2015.