FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
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DECENTRALISED PROCEDURE (FORMERLY, UK AS RMS)

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Zelys 1.25 mg Chewable Tablets for Dogs
Zelys 5 mg Chewable Tablets for Dogs
Zelys 10 mg Chewable Tablets for Dogs

Zelys vet 1.25 mg Chewable Tablets for Dogs (DK/FI/NO/SE)
Zelys vet 5 mg Chewable Tablets for Dogs (DK/FI/NO/SE)
Zelys vet 10 mg Chewable Tablets for Dogs (DK/FI/NO/SE)

DATE: 14 APRIL 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	New product n° FR/V/0356/001-003 (old procedure number UK/V/0636/001-003/DC) Change of RMS: 31 May 2018
Name, strength and pharmaceutical form	Zelys 1.25 mg Chewable Tablets for Dogs Zelys 5 mg Chewable Tablets for Dogs Zelys 10 mg Chewable Tablets for Dogs
Applicant	CEVA SANTE ANIMALE 10 avenue de la Ballastière 33500 Libourne, FRANCE
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 valve regurgitation) or dilated cardiomyopathy. 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. For the treatment of dogs with myxomatous mitral valve disease (MMVD) in the preclinical stage (asymptomatic with a systolic mitral murmur and evidence of increased heart size) to delay the onset of clinical symptoms of heart failure. (Refer to the Summary of Product Characteristics for further detail on all indications).

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic (5 mg product) and generic 'hybrid' applications (1.25 mg and 10 mg products), in accordance with Articles 13 (1) and 13 (3) respectively of Directive 2001/82/EC, as amended.
Date of completion of the original decentralised procedure	20th December 2017. National phase (FR): 13th February 2018
Date product first authorised in the Reference Member State (MRP only)	No applicable.
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden *UK added via RMS change.*

I. SCIENTIFIC OVERVIEW

These were applications for three products. Zelys 5 mg Chewable Tablets for Dogs was authorised as a generic application under Article 13 (1) of Directive 2001/82/EC, as amended. Zelys 1.25 mg and Zelys 10 mg Chewable Tablets for Dogs were authorised as generic 'hybrid' applications under Article 13 (3) of Directive 2001/82/EC, as amended. 'Hybrid' applications were determined for the 1.25 and 10 mg products because there were changes to the strength of the active substance in comparison to the reference product, Vetmedin 5 mg Flavour Tablets, marketed in the UK and expired 2014. Vetmedin 5 mg Flavour Tablets was the reference product for all proposed products. *In vivo* bioequivalence to the reference product was established for the 5 mg proposed product, and *in vitro* bioequivalence was established between the proposed 5 mg product and the 1.25 mg and 10 mg products.

Reference Products

Vetmedin 5 mg Flavour Tablets, (created from a line extension of Vetmedin 5 mg Capsules), was authorised in July 2007 and expired in November 2014. Vetmedin 5 mg Flavour Tablets was identical to a French product of equivalent name, (authorised in France in 2007), which was used in relevant bioequivalence studies.

Vetmedin 5 mg Chewable tablets was a generic of Vetmedin 5 mg Capsules, and was cited as an additional reference product, because of the established link between the two products.

The products are indicated for the treatment of canine congestive heart failure originating from valvular insufficiency (mitral and/or tricuspid valve regurgitation) or dilated cardiomyopathy. Also 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.

The product is also indicated for the treatment of dogs with myxomatous mitral valve disease (MMVD) in the preclinical stage (asymptomatic with a systolic mitral murmur and evidence of increased heart size) to delay the onset of clinical symptoms of heart failure.

Refer to the Summary of Product Characteristics (SPC), for further information on all indications.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto 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. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy[1] 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. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains 1.25 mg, 5 mg or 10 mg of pimobendan and the excipients Silica colloidal anhydrous, stearic acid, copovidone, croscarmellose sodium,

[1] Efficacy – The production of a desired or intended result.

malic acid, maize starch, cellulose microcrystalline, lactose monohydrate, dried yeast (from *Saccharonyces cerevisiae*) and pig liver powder.

The container/closure system consists of high density polyethylene screw bottles with a polypropylene child-resistant closure, a twist off cap. Bottles contain 30 tablets (10 mg product), and 60 tablets (1.25 mg and 5 mg products).
Polyamide-aluminium-polyvinyl chloride aluminium heat sealed blisters of 12, 6 or 4 tablets (1.25 mg, 5 mg and 10 mg product, respectively) are also proposed. Cardboard boxes contain 36 (1.25 mg product), 30 (5 mg product), 32 (10 mg product), or 96 tablets (1.25, 5 and 10 mg products).
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 method consists of: sieving and blending of components, followed by granulation, drying, packing, blending, tabletting and filling of tablets into bottles.

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 excipients comply with relevant Ph. Eur. monographs, apart from yeast and liver powder, which are tested against internal monographs.

Packaging materials confirm to the Certificate of Suitability, Commission Directive 10/2011 and appropriate Ph. Eur. monographs.

II.C.4. Substances of Biological Origin

Scientific data and/or 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 include those for: appearance, uniformity of mass, loss on drying, dissolution test, uniformity of dosage units, identification and assay of pimodendan, assay of impurities/degradation products and microbiological quality.

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.

II.G. Other Information

For blisters: Shelf life of the veterinary medicinal product as packaged for sale: 2 years (18 months for 5 mg and 10 mg products).

Do not store above 30 °C.

For bottle: Shelf life of the veterinary medicinal product as packaged for sale: 2 years. (18 months for 5 mg and 10 mg products).

Shelf life after first opening the immediate packaging: 2 months. (4 months for 5 mg product).

Do not store above 25ºC.

For bottle: Keep the bottle tightly closed in order to protect from moisture.
Any unused tablet portion should be returned to the bottle and be used for the next administration.
For blisters: Any unused tablet portion should be returned to the blister and be used for the next administration."

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

The products were determined to be generics/'hybrid' generic of the reference product, and as such, no toxicological or pharmacological data were required, other than a user risk assessment and environmental risk assessment.

User Safety

A user risk assessment was provided in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature are the same as those of the reference product, with an amendment of data to bring them into line with a more recent format, under the guideline EMA/CVMP/543/03-Rev. 1. Therefore the following statements are appropriate:

- Accidental ingestion, especially by a child, may lead to the occurrence of tachycardia, orthostatic hypotension, flushing of the face and headaches.
- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
- Wash hands after use.
- Close bottle tightly with cap directly after removal of the required number of tablets or part-tablets.
- Unused part-tablets should be returned to the open blister space, or to the bottle, and inserted back into the outer packaging. Keep in a safe place out of the sight and reach of children.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

The same ERA was provided for all three products and a Phase I decision tree was followed. Assessment at Phase I as the product is intended for use in non-food animals (dogs) only. When used and disposed of as recommended the products are not expected to pose a risk to the environment.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Results of a well-conducted GLP-compliant in-vivo bioequivalence study were provided comparing candidate and reference formulations (5mg products). Plasma concentrations of pimobendan were measured following a single administration.
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Animals were fasted before dosing, and sampling occurred at relevant intervals. Any deviations from protocol were noted.

Suitable statistical analyses were performed on the samples obtained, and bioequivalence was determined based on log-transformed C_{max}[2] and AUC[3].

The applicant claimed bioequivalence using a reference scaled approach with C_{max} and AUC falling within the pre-defined acceptance limits; the upper 95% confidence bound is <0 and the point estimate of the test/reference geometric mean ratio fell within the acceptance limits of 0.8-1.25.

Based on the above results, it was accepted that the proposed 5mg product has been demonstrated to be bioequivalent to the 5mg reference product.
An acceptable validation of the analytical method used to determine pimobendan concentrations in canine plasma has been provided.

A satisfactory dissolution study was performed in order to assess bioequivalence between the proposed and reference 5mg products, and thence between the

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

proposed 5mg product and proposed 1.25 mg and 10 mg products. Bioequivalence was assured upon assessment of all results.

Tolerance in the Target Species

Tolerance studies were not required due to the nature of the applications. Any adverse reactions related to the use of the product are noted within the SPC.

IV.II. Clinical Documentation

Due to the nature of the applications, no further data were 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 veterinary Heads of 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.

No significant changes in safety or efficacy data have been made after the original procedure.

The following changes in administrative or quality data were approved:

Summary of change **(Application number)**	**Section updated in Module 3**	**Approval date**
B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product (FR/V/xxxx/IA/104/G)	NA	05/04/2019
B.III.1 Update Eur. Ph. certificate of suitability to the relevant Ph. Eur. monograph from an already approved manufacturer for an active substance (FR/V/0356/001-003/IB/003)	NA	11/07/2019
Minor changes in the quantitative composition of the finished product with respect to excipient, addition of a new container (FR/V/0356/001-003/II/002/G, FR/V/0356/002-003/II/004/G)	Parts II.A, II.G and III.A	05/02/2020