Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Canergy 100 mg Tablets for Dogs

Date Created: 6th August 2015

PuAR correct as of 22/03/19 when RMS was transferred to NL. Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0542/001/DC
Name, strength and pharmaceutical form	Canergy 100 mg Tablets for Dogs
Applicant	Le Vet Beheer B.V., Wilgenweg 7, 3421 TV Oudewater, The Netherlands
Active substance(s)	Propentofylline
ATC Vetcode	QC04AD90
Target species	Dogs
Indication for use	For the improvement of peripheral and cerebral vascular blood circulation. For improvement in dullness, lethargy and overall demeanour in dogs.

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 decentralised procedure	25th March 2015
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden

I. SCIENTIFIC OVERVIEW

Canergy 100 mg tablets for dogs has been developed as a generic of Vivitonin 50 mg Tablets, in accordance with Article 13 (1) of Directive 2001/82/EC as amended. The reference product has been authorised in the UK since September 1991.

Canergy 100 mg tablets for dogs are indicated for the improvement of peripheral and cerebral vascular blood circulation and for improvement in dullness, lethargy and overall demeanour in dogs. The product is recommended to be administered at 6-10 mg propentofylline per kg bodyweight divided into two doses. Tablets can be divided into equal halves and quarters to achieve more accurate dosing. The tablets can be administered directly in the mouth, onto the back of the dog's tongue or can be mixed in a small ball of food and should be administered at least 30 minutes before feeding.

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 and 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

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

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains propentofylline and the excipients lactose monohydrate, maize starch, crospovidone, purified talc, colloidal anhydrous silica, calcium behenate, deactivated yeast and artificial beef flavour.

The container/closure system consists of ALU/PVC/PA/ALU blisters containing 10 tablets each in cartons containing 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20, 25 or 50 blister packs. The particulars of the containers and controls performed are provided and conform to the regulation.

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.

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

The manufacturing process consists of the mixing of the ingredients under dry granulation, followed by a mixing and compacting procedure. In-process controls are applied at appropriate points.

II.C. Control of Starting Materials

The active substance is propentofylline, an active substance not described in a pharmacopoeia. 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. The active substance is manufactured in accordance with an Active Substance Master File (ASMF), 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. Suitable certificates of analysis were provided assuring the quality of excipients cited in a pharmacopoeia. These all include all excipients except yeast, deactivated, and the artificial beef flavour.

II.C.4. Substances of Biological Origin

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, in order to provide assurance that lactose monohydrate and artificial beef flavour are obtained from a reliable source.

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. Tests include those for appearance, size of tablet, uniformity of units, subdivision, friability, disintegration, identity of active substance and impurities, microbial purity and tightness of blister.

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 under normal, intermediate and long-term storage. No significant changes were noted for 6 months storage at accelerated conditions, and a retest period of 48 months was supported. Long-term stability tests on the finished product and in-use product in accordance with appropriate guidelines confirmed a shelf-life of 3 years for product as packaged for sale, and 4 days for tablets in an opened package.

G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years

Shelf life of divided tablets after first opening the immediate packaging: 4 days.

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

Any unused tablet portion should be returned to the open blister and inserted back into the carton to be used for the next administration.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13 (1), and a biowaiver assuring similarity of the proposed product with the reference product was agreed, results of pharmacological and toxicological tests are 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 Documentation

The applicant provided *in vitro* studies to ascertain that the product is suitable for exemption from *in vivo* studies. This was performed in line with the Biopharmaceutics Classification System (BCS) Biowaiver (Appendix 1 of Guideline on the conduct of bioequivalence (BE) studies for veterinary medicinal products, EMA/CVMP/016/00-Rev.2). Bioequivalence was successfully claimed with the reference product (Vivitonin 100 mg tablets) and there was no requirement to provide toxicological or pharmacological data.

User Safety

A user risk assessment containing references to published literature was provided in compliance with the relevant guidelines. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Minor differences between the product and reference product were taken into account, and did not significantly affect the data with regard to user safety.

- Care should be taken to avoid accidental ingestion.
- In the event of accidental ingestion of the tablets, seek medical advice immediately and show the package leaflet or the label to the physician.
- Wash hands after use.

Environmental Safety

The product will only be used in non-food animals and as a result environmental exposure will be low. The product is not expected to cause an environmental issue when used as recommended and thus assessment ended at Phase I. A Phase II Environmental Risk Assessment (ERA) was not required.

IV CLINICAL DOCUMENTATION

A BCS biowaiver was granted for this generic product, based on the results of suitable assays provided. The criteria for approving a biowaiver for a new product are as follows:

- The active substance has been proven to exhibit high solubility and complete absorption.
- Very rapid (more than 85% within 15 minutes) in vitro dissolution characteristics of the test and reference product have been demonstrated considering specific requirements.
- Excipients that might affect bioavailability are qualitatively and quantitatively the same.

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Data were provided which matched that of the SPC for the reference product, which states that the active substance increases blood flow, and has an anti-arrhythmic effect in dogs exhibiting myocardial ischemia, and has a bronchodiliating effect similar to that of aminophylline. Plate aggregation is inhibited and the flow properties of erythrocytes improved. There is a lowering of peripheral vascular resistance in the heart and cardiac load is thereby lowered.

Pharmacokinetics

The active substance is completely absorbed and quickly distributed throughout the tissues. Maximum plasma levels are reached after 15 minutes when it is given orally to dogs. Biotransformation takes place mainly in the liver. Propentofylline is excreted in the form of its metabolites, with 80 - 90% being eliminated via the kidneys. The remainder is eliminated in the faeces.

Two GLP[3]-compliant studies were provided, one to determine the permeability characteristics of propentofylline and a validation report for the aforementioned study.

Study on the BCS classification of propentofylline

This study was designed to compare the uptake of propentofylline from the proposed and reference products, to assess the maximum solubility of the active substance at various pH and to generate dissolution profiles of the proposed and reference products at various pH.

[3] GLP – Good Laboratory Practice.

Analysis of the data produced by the permeability behaviour of the product and reference product showed little difference between the test products, assuring biocomparability. It was also determined that the active substance is not a substrate of the efflux pump. A published report was provided which confirmed that data obtained in this type of test can be used to predict *in vivo* absorption of the active substance by the means defined.

A published report was provided on the pharmacokinetic analysis of single and multiple oral doses, and intravenous (IV) administration to the dog. This was a cross-over study in four dogs, which observed the fate of two major, effective metabolites of propentofylline, as well as the location of the active substance itself.

A further study assessed the maximum solubility of 100 mg propentofylline, under suitably buffered pH conditions of 1.2, 4.5 and 7.5. The active substance was identified as being highly soluble as it dissolved in 250 ml of buffer at all relevant pH conditions. These data were extrapolated to support the conclusion that the final product was suitable for the treatment of dogs.

Dissolution profiles of the proposed and reference products were prepared, using a methodology performed under appropriate conditions. The profiles were similar and enable the proposal of the biowaiver to be accepted. Excipients used in the proposed product were accepted as being comparable to those of the reference product.

Tolerance in the Target Species

Due to the nature of the application, no further data were required for this section.

IV.II. Clinical Documentation

Laboratory Trials

Due to the nature of the application, no further data were required for this section.

Field Trials

Due to the nature of the application, no further data were required for this section.

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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