Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Soliphen

Date: 28th February 2022

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0305/001/DC
Name, strength and pharmaceutical form	Soliphen 60 mg Tablets for Dogs
Applicant	Domes Pharma 3 Rue André Citroën 63430 Pont-du-Château France
Active substance(s)	Phenobarbital
ATC Vetcode	QN03AA02
Target species	Dogs
Indication for use	Prevention of seizures due to generalised epilepsy in dogs.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original Decentralised procedure	25th February 2015
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, France, Italy, Luxembourg, Netherlands, Poland, Portugal, Spain, United Kingdom (former RMS)

I. SCIENTIFIC OVERVIEW

Soliphen 60 mg Tablets for Dogs has been developed as a generic of Epiphen 60 mg Tablets for Dogs. The reference product was first authorised in the UK in April 1996. Bioequivalence of the generic product and reference product has been accepted.

The product contains phenobarbital and is indicated for the control of epilepsy in dogs. Soliphen is contraindicated in animals with impaired hepatic function and with serious renal or cardiovascular disorders. The product should not be administered to animals weighing less than 6 kg or known to be hypersensitive to the active substance, any other barbiturates or any of the excipients.

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[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. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains phenobarbital as the active and the excipients cellulose microcrystalline, pregelatinised starch, lactose monohydrate, colloidal hydrated silica, pig liver flavour, dried yeast from *Saccharomyces* and magnesium stearate.

The container/closure system consists of a PVC/aluminium thermosealed blister of 12 tablets packaged in a cardboard box containing 5, 15 or 25 blisters. 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. The product is manufactured by mixing the phenobarbital with the excipients. The mixture is then compressed into tablets and packaged. 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 phenobarbital, an established active substance described in the European Pharmacopoeia (Ph. Eur.). A Ph. Eur. Certificate of Suitability has been provided for the active substance manufacturer. The active substance is manufactured in accordance with the principles of good manufacturing practice.

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

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.

All excipients, apart from dried yeast and pig liver powder, are described in the European Pharmacopeia and manufactured in accordance with the relevant Ph. Eur. monograph. The specifications for dried yeast and pig liver powder have been provided. Certificates of analysis have been supplied for all excipients.

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. The tests include those for identification and assay of the active substance, appearance, disintegration, dissolution, residual moisture and microbiological purity.

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 60 months has been determined.

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. Stability data are available for batches of the product stored at 25°C/60% RH for up to 36 months and at 40°C/75% RH for 6 months.

In-use stability data were also provided for the product. Tablets were broken along the divisible lines and returned to the blister pack to be stored at 25°C/60% RH for 3 days.

II.G. Other Information

- Shelf life of the finished product as packaged for sale is 3 years.
- Shelf life of divided tablets is 3 days.
- Keep the tablets in the original package. Any remaining portions of divided tablets should be replaced in the blister pocket, the blister strip should be returned to the cardboard box.
- Any tablet portions remaining after 3 days should be discarded.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required.

Toxicological Studies

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been demonstrated, results of toxicological tests are not required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the main routes of exposure would be through dermal contact and accidental hand-to-eye or hand-to-mouth contact. The risk to the end user is considered to be low if the recommended precautions are followed and will be no greater than for the reference product. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- Barbiturates can cause hypersensitivity. People with known hypersensitivity to barbiturates should avoid contact with the product.
- Accidental ingestion may cause intoxication and could be fatal, particularly for children. Take utmost care that children do not come in contact with the product.

- Phenobarbital is teratogenic and may be toxic to unborn and breastfeeding children; it may affect the developing brain and lead to cognitive disorders. Phenobarbital is excreted in breast milk. Pregnant women, women of childbearing age and lactating women should avoid accidental ingestion and prolonged skin contact with the product.
- Keep this product in its original packaging to avoid accidental ingestion.
- It is advisable to wear disposable gloves during administration of the product to reduce skin contact.
- In case of accidental ingestion, seek medical attention immediately, advising medical services of barbiturate poisoning; show the package leaflet or the label to the physician. If possible, the physician should be informed about the time and amount of ingestion, as this information may help to ensure that appropriate treatment is given.
- Each time an unused part-tablet is stored until next use, it should be returned to the open blister space and inserted back into the cardboard box.
- Wash hands thoroughly after use.

Environmental Safety

An environmental risk assessment (ERA) was conducted in accordance with VICH and CVMP guidelines.

Phase I:
The product contains phenobarbital, a barbiturate, and is for daily long term use in dogs. The product is for oral administration to a small number of individual animals. As the product will only be used in non-food animals environmental exposure will be low. A Phase II ERA was not required.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics
As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been demonstrated, no new pharmacodynamics data were required.

Pharmacokinetics
A bioequivalence study was provided comparing the test product with the reference product. The study was a two-way cross over design with a suitable number of dogs allocated to each of the treatment groups. Group 1 received the test product before the reference product and Group 2 vice versa, with a washout period between

treatments. The dogs were fasted overnight prior to oral administration of a single dose of the either the test or reference product.

Following administration of the product clinical observations were made and any adverse reactions were noted. Blood samples were taken before treatment and then at regular intervals up to 11 days after treatment. Plasma phenobarbital concentrations were determined and pharmacokinetic parameters calculated. The parameters included AUC[3], C_{max}[4] and T_{max}[5]. The data was log transformed and analysis of variance (ANOVA) performed. The 90% confidence intervals (CI) were also determined and if the intervals were within the predefined acceptance limits of 80 – 125% bioequivalence could be accepted.

The pharmacokinetic parameters for the test product were determined. The AUC was 518,866 ng/h/ml^{-1} (±85,139 ng/h/ml^{-1} SD), the C_{max} 7,400.7 ng/ml (±508.6 ng/ml SD) and the T_{max} 2.1 hours (±1.5 hours SD). For the reference product the AUC was 551,123 ng/h/ml^{-1} (±88,738 ng/h/ml^{-1} SD), the C_{max} 7,605.5 ng/ml (±696.9 ng/ml SD) and the T_{max} 2 hours (±1.9 hours SD).

The 90% CI intervals were calculated for the pivotal parameters AUC and C_{max}. For AUC these were 89.00% - 99.64% and for C_{max} they were 93.72% - 101.51%. The 90% CI fall within the predefined acceptance limits, therefore bioequivalence with the reference product can be accepted.

The tablets can be broken into quarters along score lines. Dissolution studies were not required as accurate divisibility of the tablets has been demonstrated. It is considered that the halved and quartered portions are qualitatively identical and proportional in quantities of active substance and excipients. A biowaiver has therefore been accepted.

Tolerance in the Target Species

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been demonstrated, results of tolerance studies are not required. In addition, a bioequivalence study was performed and the dogs were observed for adverse reactions. Diarrhoea was observed in two dogs during the first wash-out period and no other reactions were noted. The risk to the target species is considered to be the same as that for the reference product.

IV.II. Clinical Documentation

Laboratory Trials

[3] AUC – Area under the curve
[4] C_{max} – Maximum drug concentration
[5] T_{max} – Time to maximum concentration

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been demonstrated, results of laboratory trials are 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 Heads of Veterinary Medicinal 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.

•	03rd July 2018	Change in the RMS from UK to DE.
•	25th April 2018	Change in distributor details. From Dechra Veterinary Products Limited, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire, SY4 4AS United Kingdom to TVM UK Animal Health Limited, Crown House, 2-8 Gloucester Road, Redhill, Surrey, RH1 1FH United Kingdom.
•	30th January 2018	Deletion of a manufacturing site for an active substance manufacturer.
•	28th November 2017	Submission of an updated Ph. Eur. certificate of suitability for an active substance from an already approved manufacturer.
•	15th August 2017	Deletion of a manufacturing site responsible for secondary packaging and batch control.
•	10th November 2016	Mock-ups Approved.
•	07th September 2016	Change of MAH, from Allifax to Laboratoire TVM. Change in distributor from Allifax, France to Dechra Veterinary Products Limited, United Kingdom.
•	12th March 2021	Change in the name of the MAH from Laboratoire TVM to Domes Pharma SC; A.1 (FR/V/xxxx/IA/155/G)
•	28th February 2022	Transfer of the Marketing Authorisation from Domes Pharma SC to Domes Pharma (national procedure)