United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Phenovet 60 mg Tablets for Dogs

Date Created: 14th June 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0658/001/DC
Name, strength and pharmaceutical form	Phenovet 60 mg Tablets for Dogs
Applicant	Laboratoire TVM 57 Rue des Bardines 63370 Lempdes 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 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 conclusion of the decentralised procedure	28th February 2018
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	Austria, Germany, Ireland

I. SCIENTIFIC OVERVIEW

This was a generic application in accordance with Article 13(1) of Directive 2001/82/EC, as amended. The reference product is Epiphen 60 mg Tablets which has been authorised in the UK since April 1996.

The product is indicated for the prevention of seizures due to generalised epilepsy in dogs. The product is a white, oblong tablet, with 3 scored lines. Dogs should be dosed orally, starting with a dose of 2-5 mg per kg bodyweight per day. The dose rate should be evaluated for each individual case and depends on number, frequency, duration and severity of seizures in dogs. The dose should be divided and administered twice daily at the same time each day. The tablet can be divided into equal halves and quarters to provide 30 mg and 15 mg doses, respectively. It can take 1-2 weeks after treatment is started to reach steady state serum phenobarbital concentrations with the full effect of the medication appearing at 2 weeks. During this time the dosage should not be increased. After this time, the dosage can be increased by 20% at a time if seizures are not being controlled, up to a maximum phenobarbital serum concentration of 45 µg/ml. If the seizures are not being satisfactorily prevented at the maximum dose, then the diagnosis should be reconsidered and/or the treatment protocol amended. Plasma concentrations should be interpreted in conjunction with the observed response to therapy and a full clinical assessment including monitoring for evidence of toxic effects in each animal.

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 60 mg phenobarbital and the excipients cellulose microcrystalline, starch (pregelatinised), lactose monohydrate, silica (colloidal hydrated), pig liver flavour, dried yeast (from *Saccharomyces*) and magnesium stearate.

The container/closure system consists of a PVC/Aluminium thermosealed blister containing 12 tablets, in a box of either 5 blisters (60 tablets), 15 blisters (180 tablets) or 25 blisters (300 tablets).

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.

II.C. Control of Starting Materials

The active substance is phenobarbital, 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 and in accordance with EDQM certificate of suitability.

[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.

Excipients starch (pregelatinised), lactose monohydrate, cellulose (microcrystalline) and magnesium stearate are described in the Ph. Eur. Yeast and pig liver powder are not described in any pharmacopoeia and are controlled using thr manufacturers own specifications.

II.C.4. Substances of Biological Origin

A TSE (transmissible spongiform encephalopathy) declaration has been provided, stating that the product complies with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.
The only materials of animal origin are lactose monohydrate from milk and pig liver powder, from pork livers. A declaration is provided from the supplier of lactose monohydrate stating that milk is sourced from healthy animals in the same condition as milk collected for human consumption and that the lactose is prepared without the use of other ruminant materials other than milk and calf rennet. A declaration is provided from the supplier of the pig liver powder stating that the liver raw material is derived from pigs, which are not a TSE-relevant animal species.

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, tablet dimensions, identification of the active substance, average mass, uniformity of dosage units, disintegration, dissolution, residual moisture, friability, resistance to crushing, content of active substance, unknown impurities, and microbiological control.

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.

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

Shelf-life of the veterinary medicinal product as packaged for sale: 4 years.

Special precautions for storage:
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.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

As this was an application made in accordance with Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been demonstrated, there was no requirement for pharmacological, or toxicological data in this section. An *in vivo* bioequivalence study comparing the final product formulation of the product with the reference product was presented and is discussed in Section 4.

User Safety

A user risk assessment was provided which shows that the product is not expected to pose a risk to the user when used as recommended.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- 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

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

Phase I:
The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

As this was an application made in accordance with Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been demonstrated, there was no requirement for pre-clinical or clinical trial results. An *in vivo* bioequivalence study comparing the final product formulation of the product with the reference product was presented and is discussed below

Pharmacology

An *in vivo* bioequivalence study was provided comparing the test product with the reference product. The study was GLP compliant and was a two way cross-over design. The test and reference product were administered orally as a single dose. Dogs were fasted overnight for at least 15 hours before each treatment... The parameters for statistical analyses were AUC_{last}[3] and C_{max}[4]. Analysis of variance (ANOVA) was performed after logarithmic transformations of data. Bioequivalence between the test formulation and the reference formulation was tested with the 90% confidence intervals of the parameters. The 90% confidence intervals fell within the prespecified acceptance limits of 80 to 125%. Therefore bioequivalence between the test and reference products has been demonstrated. The applicant successfully claimed a biowaiver for authorisation of the 15 mg and 30 mg products.

[3] Area under the curve between time 0 and time of last quantifiable drug plasma concentration.
[4] Observed maximum drug plasma concentration.

Tolerance in the Target Species

As this was an application made in accordance with Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been demonstrated, it is not necessary for the applicant to provide any target species tolerance data.

IV.II. Clinical Documentation

As this was an application made in accordance with Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been demonstrated, it is not necessary for the applicant to provide any clinical documentation.

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 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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