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

Luminal vet

Date:

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0141/002/DC/
Name, strength and pharmaceutical form	Luminal vet, 100 mg, Tablets
Applicant	Desitin Arzneimittel GmbH Weg beim Jäger 214 D-22335 Hamburg, Germany
Active substance(s)	Phenobarbital
ATC Vetcode	QN03AA02
Target species	Dog
Indication for use	Treatment of idiopathic 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 32 of Directive 2001/82/EC as amended.
Date of completion of the original Decentralised procedure	29 September 2010
Date product first authorised in the Reference Member State (MRP only)	n.a.
Concerned Member States for original procedure	AT, BE, DK, ES, FR, NL, PT, SE

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. Composition

The product contains 100 mg phenobarbital per tablet and the excipients microcrystalline cellulose, maize starch, gelatin, lactose monohydrate, stearic acid (50) and colloidal anhydrous silica.

Container/closure system:
a) Brown glass containers, packed in a folding carton. Each bottle is closed with a child-resistant polyethylene stopper with bolt and bellow.
b) Plastic containers (HDPE), closed with a child resistant polypropylene screw cap and packed in a folding carton.

The particulars of the containers and controls performed are provided and conform to the regulation.

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 from 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 phenobarbital, an established active substance described in the 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.

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

D. Control on intermediate products

The tests performed during production are described and the results, 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

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.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that phenobarbital acts centrally by affecting the inhibitory neurotransmitter gamma-aminobutyric acid system.

The applicant has provided bibliographical data which show that phenobarbital is well absorbed from the gastrointestinal tract following oral administration and crosses the blood-brain barrier.

Toxicological Studies

The applicant has provided bibliographical data which show that the toxicity of Phenobarbital is well established and extensively reported.

- Single Dose Toxicity

LD50 values in rat, mouse, dog, rabbit and guinea pig range between 88 mg/kg i.p. in mouse and 284 mg/kg rectal in rat. The LD50 value in dogs after oral use is 150 mg/kg. Adverse effects which can be observed are mainly neurogenic.

- Repeated Dose Toxicity

Adverse effects reported after feeding studies or intraperitoneal administration in rodents included hepatomegaly, increased liver weight and biochemical or blood changes (e. g. induction of liver enzymes).

- Reproductive Toxicity, including Teratogenicity:

Phenobarbital is a teratogen and can produce permanent alterations in sexual maturation and may lead to sexual dysfunction in later life if used during prenatal development.

- Mutagenicity

Phenobarbital is considered to be a weak mutagen.

- Carcinogenicity (if necessary):

The carcinogenic risk of Phenobarbital for dogs is considered to be low.

Observations in Humans

PB was the first synthetic drug to be introduced for the treatment of human epilepsy in 1912, and it is the only barbiturate used as an anti-epileptic drug until today.
The applicant has provided bibliographical data which show that the most frequent adverse effect following administration of Phenobarbital in humans is sedation which after the first days of therapy usually passes without dose reduction due to the development of tolerance.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that there is a potential risk especially for pregnant or lactating women and for children after accidental ingestion.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product and to appropriately alert the user in respect to the high toxic potential in children.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the environmental concerns for this product are reduced as the product is indicated for the oral administration in dogs resulting in minimal exposure of the environment. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data which show that phenobarbital acts centrally by affecting the inhibitory neurotransmitter gamma-aminobutyric acid system. The anti-epileptic activity of phenobarbital is attributed to this interaction, while its additional sedative potency occurring at higher doses is probably related to the interaction with glutamate receptors.

The applicant has provided bibliographical data on the pharmacokinetic properties of phenobarbital showing that treatment should primarily focus on effective and safe phenobarbital plasma levels, which are between 20 and 40µg/ml according to extended experiences, rather than on a rigid dose regime.

Phenobarbital can increase its own metabolism by induction of liver enzymes.

Tolerance in the Target Species of Animals

Bibliographical data have been provided by the applicant which show that the majority of dogs can be safely treated with phenobarbital in a wide dose range and for up to many years. Clinical side effects occurring primarily at treatment initiation or at high plasma concentrations are related to the sedative potential of the compound. Severe side effects were considered exceptional.

During chronic treatment, effects of phenobarbital on the liver appear to be the rule. The change from non-toxic to toxic liver effects is difficult to determine and depends obviously on both phenobarbital plasma concentrations and treatment duration.

Most clinical side effects could be reduced when the treatment dose of phenobarbital was decreased. In order to keep all potential side-effects as low as possible, phenobarbital plasma concentrations should not exceed 40µg/ml.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies

Field Trials

The applicant has provided bibliographical data, i.e. published clinical studies and review articles which show that the recommended starting dose of 5 mg/kg phenobarbital per kg body weight in two divided doses is suitable for

the treatment of idiopathic epilepsy in dogs. The recommendation for dose adjustment based on phenobarbital serum concentrations, clinical response and the presence of side effects is well established.

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 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.

Quality changes

Summary of change **(Application number)**	**Section updated in Module 3**	**Approval date**
Change in the (invented) name of the medicinal product (DE/V/0141/IB/005/G)	Module 1	9 August 2013
Change in pack size of the finished product (additional pack sizes) (DE/V/0141/002/IB/007)	3.2.P.7 3.2.P.8	29 May 2015
Change in the immediate packaging of the finished product (addition of new container) (DE/V/0141/IB/006/G)	3.2.P.7 3.2.P.8	29 May 2015