Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Phenocoat 5 mg Film-Coated Tablets for Dogs
Phenocoat 12.5 mg Film-Coated Tablets for Dogs
Phenocoat 25 mg Film-Coated Tablets for Dogs
Phenocoat 50 mg Film-Coated Tablets for Dogs

Date Created: March 2025

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Phenocoat 5 mg Film-Coated Tablets for Dogs, Film-coated tablet Phenocoat 12.5 mg Film-Coated Tablets for Dogs, Film-coated tablet Phenocoat 25 mg Film-Coated Tablets for Dogs, Film-coated tablet Phenocoat 50 mg Film-Coated Tablets for Dogs, Film-coated tablet
Applicant	Alfasan Nederland B.V., Kuipersweg 9, 3449 JA Woerden, The Netherlands
Active substance	Phenobarbital
ATC Vet code	QN03AA02
Target species	Dogs
Indication for use	To prevent epileptic seizures and to reduce the frequency, severity and duration of seizures in idiopathic epilepsy.

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	Full application in accordance with Article 8 of VMRs 2013 (Schedule 1, Para 7) as amended.
Date of conclusion of the procedure	31/01/2025

I. SCIENTIFIC OVERVIEW

The products were submitted for a full bibliographic application, in accordance with Article 8 of VMRs 2013 (Schedule 1, Para 7) as amended.

Phenocoat film coated tablets for dogs, contain 5 mg, 12.5 mg, 25 mg or 50 mg of phenobarbital per tablet. The indication is as an anti-seizure drug for use in the management of canine idiopathic epilepsy. The starting dose is 2.5 mg of phenobarbital per kg body weight, administered twice daily. The distribution category of the product is POM-V, a veterinary medicinal product subject to prescription.

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, 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 CONSTITUENTS

II.A. Composition

The product contains phenobarbital and the excipients microcrystalline cellulose saccharin sodium, vanillin, lactose monohydrate, sodium starch glycolate (type A), magnesium stearate, colloidal hydrated silica in the core and polyvinyl alcohol, talc, titaniumdioxide (E171), iron oxide [red/yellow/black] (E172), glycerol monocarpylocaprate and sodium lauryl sulphate in the coating.

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

The container/closure system consists of PVDC/PE/PVC-PVC/Aluminium/Paper blisters containing 10 film-coated tablets in carton boxes of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or 250 tablets. 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 regulatory 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:

- Processing
- Tablet compression
- Coating

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

II.C. Control of Starting Materials

The active substance is phenobarbital, an established active substance described in the European Pharmacopoeia and is supplied in accordance with a CEP. 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.

All excipients in the formulation monographed in the European Pharmacopoeia are appropriately controlled according to their corresponding monograph. The composition and specification of the colour coating are provided and appropriate. The excipients in the colouring are controlled in accordance with the corresponding Ph. Eur. or national pharmacopoeia.

Finished product is filled into PVC/Polyethylene/PVDC-aluminium blister packs. Intermediate tablets awaiting packaging are stored in double, medium density polyethylene bags. Specifications and declarations of compliance are provided for each and are acceptable.

II.C.4. Substances of Biological Origin

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

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 are those are those appropriate for this pharmacological form.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable regulatory 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 regulatory 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 is 30 months. The product does not require any special storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

Due to the legal base of the application, as the active substance has been in well-established veterinary use for at least 10 years and an acceptable level of safety is provided, pharmacological and toxicological data obtained from the public domain has been provided.

III.A Safety Documentation

Pharmacological Studies

Bibliographical data has been provided which show that phenobarbital has an anti-epileptic effect. It acts at the central level and affects the system of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Phenobarbital has been known to inhibit spreading of seizure activity and elevate seizure threshold by binding at the GABAA-receptor. Other proposed mechanisms include

interaction with glutamate receptors to decrease neuronal excitatory postsynaptic currents and inhibition of voltage-gated calcium channels.

The applicant has provided bibliographical data which show that the absorption of phenobarbital is fairly rapid following oral administration to dogs. Peak plasma concentrations are achieved between 2 and 5 hours. Bioavailability is between 86%-96%. In dogs a difference of approximately 10% was found in absorption comparing fasted and fed dogs, suggesting that a lesser amount of the drug had been absorbed when given with the food. Phenobarbital crosses the blood-brain barrier.

In dogs, phenobarbital is primarily metabolized via the liver and has a slow elimination rate. Between individual animals the elimination half-life is between 37 and 99 hours and can therefore vary considerably. Steady-state concentrations will not be reached before 1 or 2 weeks of treatment with constant daily doses.

Toxicological Studies

The applicant has provided bibliographical data which show the below toxicological properties of phenobarbital:

- Single Dose Toxicity
  - The lowest oral LD50 for phenobarbital found by the applicant in the literature is 66 mg/kg bodyweight in rats.
- Repeated Dose Toxicity
  - No NO(A)EL (no observed adverse event level) was available, so a LOEL (lowest observed event level) of 0.8 mg/kg bodyweight, based on liver-related effects in rats, was identified from a 4-week oral dose study.
- Reproductive Toxicity, including Teratogenicity
  - For developmental toxicity, an oral NOEL (no observed event level) of 20 mg/kg bodyweight was derived, based on the occurrence of cleft palate in the offspring of mice treated at higher doses.
  - Phenobarbital is considered to be teratogenic.
- Mutagenicity
  - Phenobarbital has not been found to be genotoxic in vivo.
- Carcinogenicity
  - There is insufficient evidence to conclude that phenobarbital is carcinogenic in humans. It is carcinogenic in rats and mice, which may relate to tumour promotion, primarily in the liver and thyroid.

Observations in Humans

Bibliographical data were provided which show that phenobarbital has a long history of use in humans. The recommended therapeutic dose in humans is 60 – 80 mg/day in adults, and 1 – 1.5 mg/kg twice daily, titrated up to 2.5 – 5 mg/kg once or twice daily, in children. Adverse effects are mostly neurological, including sedation, mood changes, and impairment of cognition and memory.

Hypersensitivity reactions have been reported, and phenobarbital is excreted in breastmilk.

The target species for this product is dogs.

User Safety

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

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:

- Phenobarbital may cause serious effects, such as sedation, disorientation, ataxia, nystagmus, and can be fatal after accidental ingestion by children. To avoid accidental ingestion, take utmost care that children do not come in contact with the film-coated tablets. The tablets should be carefully kept away from children. Keep the tablets in the original packaging prior to use.
- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Environmental Safety

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

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

Due to the legal base of the application, bibliographical data has been provided to document the clinical use of phenobarbital.

IV.I. Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data describing the pharmacodynamic and pharmacokinetic properties of the active substance.

Phenobarbital is recognised as a first line therapy and long-term treatment in the management of canine epilepsy. In veterinary medicine, phenobarbital has been used extensively in dogs for more than 50 years as an anti-seizure drug for the management of idiopathic epilepsy. It has the longest history of chronic use of all anti-epileptic drugs in veterinary medicine and available data suggest that phenobarbital is the most effective anti-epileptic drug currently used in veterinary medicine. Phenobarbital has been reported to be effective in decreasing seizure

frequency in approximately 60−93% of dogs with idiopathic epilepsy, when plasma concentrations are maintained within the therapeutic range of 25−35 µg/ml.

GABA is the major inhibitory neurotransmitter of the central nervous system. Phenobarbital binds at the GABA receptor, thereby enhancing neuronal inhibition. Other mechanisms of action of phenobarbital include a direct interaction with glutamate receptors to decrease neuronal excitatory postsynaptic currents, inhibition of voltage-gated calcium channels resulting in decreased calcium influx in neurons and competitive binding with the picrotoxin site of the chloride channel. Overall, phenobarbital increases the seizure threshold and decreases the spread of discharge to surrounding neurons.

Regarding pharmacokinetics the applicant provided bibliographical information from laboratory animals, humans and dogs. Due to product data provided by the applicant, it is concluded that the pharmacokinetic profile of the phenobarbital products used in the literature provided, are representative of the test product and should demonstrate similar target species efficacy. In dogs the pharmacokinetics of oral and intravenous routes have been studied, and it has been found that absorption occurs within 2 hours. Oral bioavailability is high, estimated at 86-89% and phenobarbital is known to cross the blood-brain barrier. Phenobarbital is primarily metabolised via the liver, although 25% of the unchanged drug is eliminated by pH-dependent renal excretion. Phenobarbital was demonstrated to have a fairly slow elimination rate and steady state concentrations are not reached until after 1-2 weeks of treatment.

Tolerance in the Target Species

The applicant has provided bibliographical data that details the toxicity of phenobarbital, regarding accidental overdose, repeated dose toxicity as well as target animal tolerance in clinical studies. The majority of dogs can be safety treated with phenobarbital long-term, covering a wide dose range.

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

IV.II. Clinical Documentation

Laboratory and Field Trials

The applicant has provided bibliographical data which show that phenobarbital is a well-known, effective anticonvulsant and is generally considered the medication of choice for initiating anticonvulsant therapy in dogs. The data submitted covers from 1980 to 2023.

A controlled study was done in dogs with epilepsy at the Veterinary Hospital of the University of Pennsylvania, authored by Farnbach, titled ‘Serum concentrations and efficacy of phenytoin, phenobarbital, and primidone in canine epilepsy’. It was found that phenobarbital was effective at serum concentrations

of 14 to 45 µg/ml and 20 of 42 dogs given phenobarbital became seizure free. Many subsequent studies have been performed, meaning the therapeutic range of phenobarbital blood concentrations is well established at 25-30 µg/ml, which is achieved by the administration of 5-11 mg/kg or higher.

The starting dose of the product is 2.5 mg/kg which is supported by the literature, showing that the starting dose of phenobarbital should be between 2 to 3 mg/kg twice a day. It is recommended that the dose of the product is increased in steps of 20% at a time, with associated monitoring of phenobarbital levels which is also demonstrated in the bibliographical data.

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.

(www.gov.uk/check-animal-medicine-licensed)

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.

(www.gov.uk/check-animal-medicine-licensed)