



**Veterinary
Medicines
Directorate**

**United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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NATIONAL PROCEDURE

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY
MEDICINAL PRODUCT**

**Phenosan 12.5 mg Chewable Tablets for Dogs
Phenosan 50 mg Chewable Tablets for Dogs
Phenosan 100 mg Chewable Tablets for Dogs**

Date Created: February 2025

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Phenosan 12.5 mg Chewable Tablets for Dogs Phenosan 50 mg Chewable Tablets for Dogs Phenosan 100 mg Chewable Tablets for Dogs
Applicant	Alfasan Nederland B.V., Kuipersweg 9, 3449 JA Woerden, The Netherlands
Active substance	Phenobarbital
ATC vet code	QN03AA02
Target species	Dogs
Indications 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 bibliographic application in accordance with Article 8 of VMRs 2013 (Schedule 1, Para 7) as amended.
Date of conclusion of the procedure	04/02/2025

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.

Phenosan chewable tablets for dogs, contain 12.5 mg, 50 mg or 100 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 is POM-V, 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 efficacy² 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; magnesium stearate; sodium starch glycolate (type A); lactose monohydrate; vanillin; saccharin sodium; and silica, colloidal hydrated.

¹ SPC – Summary of product Characteristics.

² Efficacy – The production of a desired or intended result.

The container/closure system consists of blister packs containing 10 tablets in a cardboard box. 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 product is manufactured in accordance with the European Pharmacopoeia and relevant regulatory guidelines.

II.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 and is supplied in accordance with a CEP. Batch analytical data demonstrating compliance with this specification have been provided.

All excipients in the formulation are monographed in the European Pharmacopoeia and are appropriately controlled according to their corresponding monograph.

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

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. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specification. Control tests on the finished product 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

The shelf life of the product as packaged for sale is 30 months. The product does not require any special storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACOTOXICOLOGICAL)

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

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 metabolised 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 bw.
- Repeated Dose Toxicity
 - For repeated dose toxicity, no NO(A)EL was available, so a LOEL of 0.8 mg/kg bw based on liver-related effects in rats was identified from a 4-week oral dose study in rats.
- Reproductive Toxicity, including Teratogenicity
 - For developmental toxicity, an oral NO(A)EL of 20 mg/kg bw was derived based on the occurrence of cleft palate in the offspring of mice at higher doses.
 - Phenobarbital is considered to be teratogenic.
- Mutagenicity
 - Phenobarbital has not been found to be genotoxic in vivo.
- Carcinogenicity (if necessary):
 - There is insufficient evidence to conclude that phenobarbital is carcinogenic in humans. Phenobarbital has been shown to be 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 been used in humans for approximately 100 years. 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 guidelines.

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 in children. To avoid accidental ingestion, take utmost care that children do not come in contact with the tablets or unused tablet parts.
- Care should be taken to avoid prolonged dermal contact, including hand-to-mouth contact.
- Do not smoke, eat or drink during use of the product.
- In case of accidental ingestion, seek medical advice immediately and show the pack-age leaflet or the label to the physician.
- Phenobarbital and vanillin may cause a hypersensitivity reaction. People with known hypersensitivity to phenobarbital or vanillin should avoid contact with the veterinary medicinal product. Seek medical advice in case of severe hypersensitivity reactions.
- Phenobarbital is teratogenic and may be toxic to unborn and breastfed 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 women who are breastfeeding should avoid dermal contact with the veterinary medicinal product, including hand-to-mouth contact.
- It is advisable to wear disposable gloves during administration of the veterinary medicinal product.
- Wash hands 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

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

IV.I. Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographic data describing the pharmacodynamic and pharmacokinetic properties of phenobarbital.

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.

GABA is the major inhibitory neurotransmitter of the central nervous system and 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 excitation, inhibition of voltage-gated calcium channels 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.

In dogs the pharmacokinetics of oral and intravenous routes of phenobarbital administration have been studied. After ingestion, peak plasma concentration was achieved between 2 and 5 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 renal excretion.

Tolerance in the Target Species

The applicant has provided bibliographical information detailing the toxicity of phenobarbital, accidental overdose, repeated dose toxicity as well as target animal tolerance in clinical studies. The data presented on target animal safety and the adverse effects when using phenobarbital are well described. The majority of dogs can be safely treated with phenobarbital covering a wide dose range, and for long term treatment.

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 from 1980 to 2023 which show that phenobarbital is a well know effective anticonvulsant and is generally considered the medication of choice for initiating anticonvulsant therapy in dogs.

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.

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 products are 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.

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