SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Phenocoat 5 mg film-coated tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Active substance:

Phenobarbital 5 mg

Excipients:

Qualitative composition of excipients and other constituents
Core:
Microcrystalline cellulose
Saccharin Sodium
Vanillin
Lactose monohydrate
Sodium starch glycolate (type A)
Magnesium stearate
Silica, colloidal hydrated
Coating:
Poly(vinyl alcohol)
Talc
Titanium dioxide (E171)
Glycerol monocaprylocaprate
Sodium laurilsulfate
Iron oxide (E172): Pigment: Pink: Iron oxide black, Iron oxide red

5 mg: Pink film-coated tablet with a deep concave shape.

3. CLINICAL INFORMATION

3.1 Target species

Dogs.

3.2 Indications for use for each target species

To prevent epileptic seizures and to reduce the frequency, severity and duration of seizures in idiopathic epilepsy.

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or other barbiturates.
Do not use in animals with severe liver disease, serious renal or cardiovascular disorders.

3.4 Special warnings

The decision to start antiepileptic drug therapy with phenobarbital should be evaluated for each individual case and depends on number, frequency, duration and severity of seizures in dogs
Early treatment is warranted because repetitive seizures may create additional seizure foci.
Therapeutic phenobarbital serum concentrations should be monitored to enable the lowest effective dose to be used. The individual variability in phenobarbital metabolism is high. Due to auto-induction of hepatic microsomal enzymes (see section 4.3 pharmacokinetics) increasing dose increments might be necessary over time to maintain the same serum concentration.
Some of the dogs are free of epileptic seizures during the treatment, but some of the dogs show only a seizure reduction, and some of the dogs are considered to be non-responders.

3.5 Special precautions for use

<u>Special precautions for safe use in the target species:</u>
Caution is required in animals with impaired liver and / or renal function, hypovolaemia, anemia and cardiac or respiratory dysfunction.
It is recommended that the clinical pathology (haematology and clinical chemistry, including hepatic function and thyroid function) of the patient is evaluated prior to initiation of therapy and monitored 2-3 weeks after initiation of therapy and subsequently every 4-6 months.
The chance of hepatotoxic side effects can be diminished or delayed using an effective dose that is as low as possible.
In the case of suspected hepatotoxicity, liver function tests are recommended. In case of acute hepatic failure or chronic liver cell damage phenobarbital must be discontinued and replaced by another type of antiepileptic therapy.
Withdrawal of phenobarbital or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures.

In stabilized epileptic patients, caution should be taken when switching between phenobarbital formulations

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
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.

Special precautions for the protection of the environment:
Not applicable.

3.6 Adverse events

Dogs:

Very common (>1 animal / 10 animals treated):	polyphagia[1], polydipsia[1], lethargy[1], polyuria, sedation[1], ataxia[1], elevated liver enzymes[2].
Common (1 to 10 animals / 100 animals treated):	hyperexcitation[3].
Uncommon (1 to 10 animals / 1,000 animals treated):	blood dyscrasia (such as anaemia, and/or thrombocytopenia, and/or neutropenia) [4], hypoalbuminaemia[4], elevated serum lipids, dyskinesia[4], anxiety[4], hepatic toxicosis[5], pancreatitis.
Undetermined frequency (cannot be estimated from available data)	diarrhoea, emesis, dermatitis[6], low thyroxine (T4)[7].

[1] These effects are usually transitory (10-21 days) and disappear with continued medication.
[2] These may be associated with non-pathological changes, but could also represent hepatotoxicity.
[3] Particularly observed after initiation of therapy. As this hyperexcitation is not linked to overdosage, no reduction of dosage is needed.
[4] Reversible with reduction of dosage or discontinuation of phenobarbital therapy.

[5] Associated with long-term use of phenobarbital and high therapeutic doses (> 20 mg/kg/day) or high serum concentrations (≥ 35 µg/ml). Any changes are reversible with discontinuation of the drug if identified early in the course of disease.
[6] Superficial necrolytic dermatitis as part of the anticonvulsant hypersensitivity syndrome (AHS).
[7] Lower total T4 or free T4 serum levels may not be an indication of hypothyroidism. Treatment with thyroid hormone replacement should only be started if there are clinical signs of the disease.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation in dogs.

Pregnancy:
Studies have shown that phenobarbital crosses the placenta in laboratory animals and humans. Studies in laboratory animals have shown evidence for teratogenic and developmental effects. Phenobarbital has an effect during prenatal growth, in particular causing permanent changes in neurological and sexual development.
Use only according to the benefit-risk assessment by the responsible veterinarian. The risk that the medication may cause an increase in the number of congenital defects must be weighed up against the risk of suspending treatment during pregnancy.

Lactation:
Studies in laboratory animals and humans have shown that phenobarbital is excreted in milk. Pups should be monitored carefully for pharmacological effects such as sedation. If somnolence/sedative effects (that could interfere with suckling) appear in nursing newborns, an artificial suckling method should be chosen.
Use only according to the benefit-risk assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

Phenobarbital induces both plasma proteins such as α1-acid glycoprotein and hepatic microsomal cytochrome P450 (CYP) enzymes which can lead to drug-drug interactions. Therefore special attention must be paid to the pharmacokinetics and doses of drugs administered simultaneously.

The induction of plasma proteins results in an increased binding to plasma proteins and thus a lower unbound fraction of substances in plasma. The induction of CYP enzymes may result in a higher metabolism of substances metabolized by these enzymes, and thus a lower concentration of substances in plasma, including phenobarbital itself.

The therapeutic effect of benzodiazepines, such as diazepam, may be decreased in animals which are treated chronically with phenobarbital. This is particularly important in cases of *status epilepticus* in animals treated chronically with phenobarbital.

The plasma concentrations and thus the therapeutic effects of other anti-epileptic drugs, such as levetiracetam and zonisamide, may be decreased by phenobarbital when used simultaneously.
Phenobarbital is synergistic with other GABA-ergic drugs such as bromide.

As phenobarbital is partially metabolized by CYP enzymes, substances that inhibit CYP enzyme activity, may cause an increased plasma concentration of phenobarbital. Several substances have been identified as CYP inhibitors in humans and laboratory animals and/or *in-vitro* studies. The clinical impact of these interactions is considered low when these substances are used at therapeutical doses, however possible interactions cannot be excluded completely. Examples of such substances are: ketoconazole, griseofulvin, chloramphenicol, α2-agonist such as medetomidine and xylazine, atipamezole, propofol.

3.9 Administration routes and dosage

Oral use.
The recommended starting dose is 2.5 mg phenobarbital per kg body weight, administered twice daily q12h (every 12 hours).
To ensure a correct starting dosage, body weight should be determined as accurately as possible.
Tablets must be given at the same time each day to achieve successful therapy.
Steady state serum concentrations are not reached until 1-2 weeks after treatment is initiated, and therefore initial efficacy of the medication may vary and doses should not be increased during this time.
Any adjustments to the starting dose are best made on the basis of clinical efficacy, blood concentrations of phenobarbital and the occurrence of adverse events.

Determining serum phenobarbital concentration is essential for providing appropriate therapy, the time to reach steady state (1-2 weeks) and increased metabolism due to auto-induction (6 weeks) should be kept in mind when determining a serum concentration monitoring plan.
The phenobarbital concentrations considered therapeutically effective vary from 15 to 40 µg/ml, but in most dogs, serum phenobarbital concentration between 25−30 µg/ml is required for optimal seizure control.
Due to differences in the excretion of phenobarbital and differences in sensitivity, the effective doses may vary considerably between patients (from 1 mg to 15 mg/kg body weight twice a day).
In case of insufficient therapeutic efficacy, the dosage can be increased in steps of 20% at a time, with associated monitoring of serum phenobarbital concentrations.
Due to auto-induction of hepatic microsomal enzymes, in some dogs phenobarbital half-life can become shorter than 20h after chronic treatment. In those cases, to minimize therapeutically relevant fluctuation of serum concentrations, an 8-h dosing interval could be considered.
If the seizures are not being satisfactorily prevented and if the maximum level concentration is about 40 µg/ml, then the diagnosis should be reconsidered and/or a second antiepileptic product should be added to the treatment protocol.

Plasma concentrations should always 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.

Please note that this dosing table is intended as a guide for dispensing the veterinary medicinal product at the recommended starting dose for each administration: 2.5 mg/kg. It states the number and type of tablets required to administer 2.5 mg phenobarbital per kg bodyweight per administration.

Body weight	Phenocoat 5 mg		Phenocoat 12.5 mg	Phenocoat 25 mg		Phenocoat 50 mg
2 kg	●					
4 kg	● ●					
5 kg			●			
7 kg	●	AND	●			
10 kg				●		
20 kg						●
30 kg				●	AND	●
40 kg						● ●
50 kg				●	AND	● ●
60 kg						● ● ●

A suitable combination of tablet sizes should be used in order to administer the optimal dosage for each dog.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

Symptoms of overdose are:
- depression of the central nervous system demonstrated by signs ranging from sleep to coma,
- respiratory compromise,
- cardiovascular compromise, hypotension and shock leading to renal failure and death.

In case of overdose remove ingested tablets from the stomach, and give respiratory and cardiovascular support as necessary.
The prime objectives of management are intensive symptomatic and supportive therapy with particular attention being paid to the maintenance of cardiovascular, respiratory and renal functions and to the maintenance of the electrolyte balance.
There is no specific antidote, but clearance of phenobarbital can be enhanced by hemodialysis or peritoneal dialysis.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QN03AA02.

4.2 Pharmacodynamics

Phenobarbital is a phenyl barbiturate with an anti-epileptic effect. Phenobarbital operates 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 $GABA_A$-receptor, thus both directly activating GABA receptor-gated chloride channels and increasing the affinity of GABA for its own receptor by allosteric effect.
Other proposed mechanisms include interaction with glutamate receptors to decrease neuronal excitatory postsynaptic currents and inhibition of voltage-gated calcium channels.

4.3 Pharmacokinetics

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.

The volume of distribution is ~700 ml/kg. Plasma protein binding is between 45 and 60 % depending on the plasma drug concentration. Phenobarbital crosses the blood-brain barrier. The ratio between cerebrospinal fluid and total plasma concentrations is almost equal to the free fraction of drug in plasma.

In dogs, phenobarbital is primarily metabolized via hepatic microsomal enzymes, although up to 25% of the unchanged drug is eliminated by pH-dependent renal excretion.

Phenobarbital 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.

Phenobarbital is a potent inducer of hepatic microsomal cytochrome P450 (CYP450) enzymes. As a result, after chronic phenobarbital administration, phenobarbital can induce its own metabolism resulting in an increased total body clearance and shorter elimination half-life.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 30 months

5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

5.4 Nature and composition of immediate packaging

PVDC/PE/PVC-PVC/Aluminium/Paper blister containing 10 film-coated tablets.
Carton box containing 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or 250 film-coated tablets.

Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Alfasan Nederland B.V.

7. MARKETING AUTHORISATION NUMBER

Vm 36408/3046

8. DATE OF FIRST AUTHORISATION

02 October 2024

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

October 2024

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

Gavin Hall
Approved: 25 November 2024