ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARTON BOX

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Phenocoat 5 mg film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCES

Phenobarbital 5 mg/tablet

3. PACKAGE SIZE

10 tablets
20 tablets
30 tablets
40 tablets
50 tablets
60 tablets
70 tablets
80 tablets
90 tablets
100 tablets
250 tablets

4. TARGET SPECIES

Dogs

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Oral use

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp. {mm/yyyy}

9. SPECIAL STORAGE PRECAUTIONS

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Accidental ingestion of these tablets by children can be harmful. Read the package leaflet before use.

11. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

12. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

Alfasan Nederland B.V.

14. MARKETING AUTHORISATION NUMBERS

Vm 36408/3046

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PVC/PE/PVDC-PVC/Aluminium/Paper blister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Phenocoat

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Phenobarbital 5 mg/tablet

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Phenocoat 5/12.5/25/50 mg film-coated tablets for dogs

2. Composition

Each film-coated tablet contains:

Active substance:

Phenobarbital 5/12.5/25/50 mg

5 mg: Pink film-coated tablet with a deep concave shape
12.5 mg: Yellow film-coated tablet with a modified ball shape
25 mg: Orange film-coated tablet with a modified ball shape
50 mg : Brown film-coated tablet with a modified ball shape

3. Target species

Dogs.

4. Indications for use

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

5. 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.

6. Special warnings

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 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.

Special precautions for safe use in the target species:
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.

Pregnancy and lactation:
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.

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.

Overdose:
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 product 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.

Major incompatibilities:
Not applicable

7. 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 product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder or the local representative of the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system:

8. Dosage for each species, routes and method of administration

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.
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 a correct 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 induction of hepatic microsomal enzymes, in some dogs phenobarbital half-life becomes 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.

9. Advice on correct administration

Tablets must be given at the same time each day to achieve successful therapy.

10. Withdrawal periods

Not applicable.

11. Special storage precautions

Keep out of the sight and reach of children.

This veterinary medicinal product does not require any special storage conditions. Do not use this veterinary medicinal product after the expiry date which is stated on the blister after Exp. The expiry date refers to the last day of that month.

12. Special precautions for disposal

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 applicable national collection systems. These measures should help to protect the environment. Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

Vm 36408/3046
Vm 36408/3047
Vm 36408/3048
Vm 36408/3049

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.

15. PID LINK (Do not print heading)

[The following statement must be included where reference to the European Union Product Database is included on the product information. This statement is relevant to both UK(GB) and UK(NI) products:]

Find more product information by searching for the 'Product Information Database' on www.gov.uk.

16. Contact details

Marketing authorisation holder and manufacturer responsible for batch release and contact details to report suspected adverse reactions:
Alfasan Nederland B.V.
Kuipersweg 9
3449 JA Woerden
The Netherlands

Manufacturer responsible for batch release
Lelypharma B.V.
Zuiveringweg 42
8243 PZ Lelystad
The Netherlands

Local representatives and contact details to report suspected adverse reactions:

17. Other information

Gavin Hall
Approved: 25 November 2024