

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARDBOARD BOX

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Phenoleptil 50 mg Tablets for dogs
Phenobarbital

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains
Phenobarbital 50 mg

3. PHARMACEUTICAL FORM

Tablet

4. PACKAGE SIZE

50 tablets
100 tablets
250 tablets
500 tablets
1000 tablets

5. TARGET SPECIES

Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral administration.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Not applicable.

9. SPECIAL WARNING(S), IF NECESSARY

10. EXPIRY DATE

EXP {month/year}

Shelf-life after first opening of the immediate packaging: 24 hours.
Divided tablets should be stored in the blister pack. Any divided tablet portions remaining after 24 hours should be discarded.

11. SPECIAL STORAGE CONDITIONS

Keep the container in the outer carton in order to protect from light

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dechra Regulatory B.V.
Handelsweg 25
5531 AE Bladel
The Netherlands

16. MARKETING AUTHORISATION NUMBER(S)

Vm 50406/4024

17. MANUFACTURER’S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

(BLISTER)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Phenoleptil 50 mg Tablets for dogs
Phenobarbital

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dechra Regulatory B.V.

3. EXPIRY DATE

EXP {MM/YY}

4. BATCH NUMBER

Lot {number}

5. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Phenoleptil 50 mg Tablets for dogs

**1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
AND OF THE MANUFACTURING AUTHORISATION HOLDER
RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT**

Marketing authorisation holder:

Dechra Regulatory B.V.
Handelsweg 25
5531 AE Bladel
The Netherlands

Manufacturer responsible for batch release:

LelyPharma B.V.
Zuiveringsweg 42
8243 PZ Lelystad
The Netherlands

Genera Inc.
Svetonedeljska cesta 2, Kalinovica
10436 Rakov Potok
Croatia

Only the site testing and releasing the batches will be mentioned on the printed leaflet.

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Phenoleptil 50 mg Tablets for dogs
Phenobarbital

**3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER
INGREDIENT(S)**

Each white to off white biconvex tablet with brown speckles and a score line on one side (diameter 9 mm) contains phenobarbital 50 mg. The tablet can be divided into two equal parts.

4. INDICATION(S)

Prevention of seizures due to generalised epilepsy in dogs.

5. CONTRAINDICATIONS

Do not use in case of hypersensitivity to the active substance or any other barbiturates.

Do not use in animals with serious impaired hepatic function.

Do not use in animals with serious renal or cardiovascular disorders.

6. ADVERSE REACTIONS

During start of therapy ataxia, sleepiness, slackness and dizziness can occur but these effects are usually transitory and disappear in most, but not all, patients with continued medication.

Some animals can demonstrate a paradoxical hyperexcitability, particularly after first starting therapy.

As this hyperexcitability is not linked to overdosage, no reduction of dosage is needed.

Polyuria, polydipsia and polyphagia can occur at average or higher therapeutic active serum concentrations; these effects can be diminished by limiting intake of both food and water.

Sedation and ataxia often become significant concerns as serum levels reach the higher ends of the therapeutic range.

High plasma concentrations may be associated with hepatotoxicity.

Phenobarbital can have deleterious effects on stem cells from bone marrow.

Consequences are immunotoxic pancytopenia and/or neutropenia. These reactions disappear after the treatment's withdrawal.

Treating dogs with phenobarbital may lower their TT4 or FT4 serum levels, however this may not be an indication of hypothyroidism. Treatment with thyroid hormone replacement should only be started if there are clinical signs of the disease.

If adverse effects are severe, the decrease in the administered dose should be recommended.

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Administration route

Oral.

Amounts to be administered

The recommended initial dosage is 2,5 mg phenobarbital per kg body weight twice daily.

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

Eventual adjustments of this dosage should be made on the basis of clinical efficacy, blood levels and the occurrence of undesirable side effects.

9. ADVICE ON CORRECT ADMINISTRATION

The serum phenobarbital concentrations should be measured after steady state has been achieved. The ideal therapeutic range for serum phenobarbital concentration is between 15 and 40 µg/ml. If serum phenobarbital concentration is less than 15 µg/ml or the seizures are not controlled the dose may be increased by 20% at a time, with associated monitoring of serum phenobarbital levels up to a maximum serum concentration 45 µg/ml. The ultimate doses may vary considerably (ranging from 1

mg to 15 mg per kg body weight twice daily) because of the differences in phenobarbital excretion and differences in sensitivity among patients. If the seizures are not being satisfactorily controlled and if the maximum level concentration is about 40µg/ml, then the diagnosis should be reconsidered and/or a second antiepileptic product (such as bromides) should be added to the treatment protocol.

In stabilised epileptic patients, it is not recommended to switch from other phenobarbital formulations to Phenoleptil 12.5 mg or 50 mg Tablets. However, if this can not be avoided then additional caution should be taken. It is recommended to try to achieve as similar dosages as possible compared with the previous formulation used taking into consideration current plasma concentration measurements. Stabilisation protocols as for initiating treatments should be followed. Also see section 12).

For accuracy of dosing, dogs under 10 kg should commence therapy with Phenoleptil 12.5 mg Tablets.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Keep the container in the outer carton in order to protect from light.

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

Do not use after expiry date stated on the blister and carton after EXP. The expiry date refers to the last day of that month.

Any divided tablet portions remaining after 24 hours should be discarded.

Divided tablets should be stored in the blister pack.

12. SPECIAL WARNING(S)

Special warnings for each target species:

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.

General recommendations for initiating therapy include a single seizure occurring more than once every 4-6 weeks, cluster seizure activity (i.e. more than one seizure within 24 h) or status epilepticus regardless of frequency.

To achieve successful therapy, administration of tablets must be at the same time each day.

Withdrawal or transition from other types of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures.

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 use in animals:

Caution is recommended in animals with impaired hepatic and renal function, hypovolemia, anaemia and cardiac or respiratory dysfunction.

The chance of hepatotoxic side effects can be diminished or delayed using an effective dose that is as low as possible. Monitoring of hepatic parameters is recommended in case of a prolonged therapy.

It is recommended to assess the clinical pathology of the patient 2-3 weeks after start of treatment and afterwards every 4-6 months, e.g. measurement of hepatic enzymes and serum bile acids. It is important to know that the effects of hypoxia etc. do cause increased levels of hepatic enzymes after a seizure.

Phenobarbital may increase the activity of serum alkaline phosphatase and transaminases. These may demonstrate non-pathological changes, but could also represent hepatotoxicity. Therefore, in the case of suspected hepatotoxicity, liver function tests are recommended. Increased liver enzyme values do not require a dose reduction of Phenobarbital if the serum bile acids are in the normal range. Monitoring of hepatic parameters is recommended in case of a prolonged therapy, because of phenobarbital's hepatotoxicity.

In stabilised epileptic patients, it is not recommended to switch from other phenobarbital formulations to Phenoleptil 12.5 mg or 50 mg Tablets. However, if this cannot be avoided then additional caution should be taken. This includes more frequent plasma concentration sampling to ensure that therapeutic levels are maintained. Monitoring for increased side effects and for hepatic dysfunction should be conducted more regularly until stabilisation is confirmed.

Withdrawal of therapy with Phenobarbital formulations should be made gradually to avoid precipitating an increase in the frequency of seizures.

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

People with known hypersensitivity to barbiturates should avoid contact with the veterinary medicinal product. Wash hands after use.

Take utmost care that children do not come into contact with the product. Children are particularly at risk of intoxication which may prove fatal.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. If possible, the physician should be informed about the time and amount of ingestion, as this information may help to ensure that appropriate treatment is given.

Pregnancy and lactation:

Phenobarbital crosses the placental barrier and at higher doses (reversible) withdrawal symptoms in new-borns cannot be excluded. Studies in laboratory animals have shown evidence of action of phenobarbital on prenatal growth, especially concerning sexual development. Neonatal bleeding tendencies have been associated with phenobarbital treatment during pregnancy. Administration of Vitamin K to the dam for 10 days before parturition may help to minimize these effects on the fetus.

The safety of the veterinary medicinal product has not been established during pregnancy of dogs. The benefits of treatment may be greater than the potential risks associated with epileptic seizures on the fetus (hypoxia and acidosis). Therefore, in case of pregnancy, termination of antiepileptic treatment is not recommended; however, the dose should be as low as possible.

Phenobarbital is excreted in small amounts in breast milk and during nursing pups should be monitored carefully for undesired sedative effects. Weaning early may be an option. If somnolence/sedative effects (that could interfere with suckling) appear in nursing new-borns, an artificial suckling method should be chosen.

Use during pregnancy and lactation only accordingly to the benefit/risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction:

A therapeutic dose of phenobarbital for antiepileptic therapy can significantly induce plasma protein (such as α 1acid glycoprotein, AGP), which bind drugs. Therefore special attention must be paid to the pharmacokinetics and doses of drugs simultaneously administered.

The plasmatic concentration of cyclosporine, thyroid hormones and theophylline is decreased in the case of concurrent administration of phenobarbital. The effectiveness of these substances is diminished too.

Cimetidine and ketoconazole are inhibitors of hepatic enzymes: concurrent use with phenobarbital can induce an increase of serum concentration of phenobarbital.

Concurrent use with potassium bromide increases the risk of pancreatitis.

Concurrent use with other drugs having a central depressive action like narcotic analgesics, morphinic derivatives, phenothiazines, antihistamines, clomipramine and chloramphenicol can decrease the effect of phenobarbital.

Phenobarbital may enhance the metabolism of, and therefore decrease the effect of, antiepileptics, chloramphenicol, corticosteroids, doxycycline, beta blockers and metronidazole.

The reliability of oral contraceptives is lower.

Phenobarbital may decrease the absorption of griseofulvin.

The following drugs can decrease the convulsive threshold: quinolones, high doses of β -lactam antibiotic, theophyllin, aminophyllin, cyclosporine and propofol (for example). Medications which may alter the seizure threshold should only be used if really necessary and when no safer alternative exists.

Overdose (symptoms, emergency procedures, antidotes):

Symptoms of overdose are:

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

In case of overdose remove ingested product from the stomach, for example by lavage. Activated charcoal may be given. Offer respiratory support.

There is no specific antidote, but CNS stimulants (like Doxapram) may stimulate the respiratory centre. Give oxygen support.

Incompatibilities:

Not applicable.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

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

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

December 2022

15. OTHER INFORMATION

Pharmacodynamic properties

The antiepileptic effects of phenobarbital are probably the result of at least two mechanisms, being decreased monosynaptic transmission, which presumably results in reduced neuronal excitability and an increase in the motor cortex's threshold for electrical stimulation.

Pharmacokinetic particulars

After oral administration of phenobarbital to dogs, the drug is rapidly absorbed and maximal plasma concentrations are reached within 4-8 hours. Bioavailability is between 86%-96%, apparent volume of distribution is 0,75 l/kg and a steady state serum concentration is reached 2-3 weeks after start of therapy.

About 45% of the plasma concentration is protein bound. Metabolism is by aromatic hydroxylation of the phenyl group in the para position (p-hydroxyphenobarbital), and about 25% of the drug is excreted unchanged in the urine. Elimination half-lives vary considerably between individuals and range from about 40-90 hours.

Package (size)

Aluminium/PVC strips with 10 tablets packed in cardboard boxes with 5, 10, 25, 50 or 100 strips.

Aluminium/PVC/PE/PVdC strips with 10 tablets packed in cardboard boxes with 5, 10, 25, 50 or 100 strips.

Not all pack sizes may be marketed.

Approved 03 February 2023

