ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

(OUTER CARTON / CARDBOARD BOX)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Phenoleptil 25 mg Tablets for dogs
Phenobarbital

2. STATEMENT OF ACTIVE SUBSTANCES

Phenobarbital 25 mg

3. PHARMACEUTICAL FORM

Tablet.

4. PACKAGE SIZE

100 tablets
500 tablets

5. TARGET SPECIES

Dogs.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

People with known hypersensitivity to barbiturates should avoid contact with this product.
Children are particularly at risk of intoxication which may prove fatal. Take utmost care that children do not come into contact with the product.

10. EXPIRY DATE

EXP {month/year}
Return any divided tablets to the opened blister pack and use within 48 hours.

11. SPECIAL STORAGE CONDITIONS

Do not store above 30oC.
Keep the container in the outer package 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 50406/4025

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

(BLISTER)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Phenoleptil 25 mg Tablets for dogs
Phenobarbital

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dechra Regulatory B.V.

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Lot {number}

5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
PHENOLEPTIL 25 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:
Name: Dechra Regulatory B.V.
Address: Handelsweg 25
5531 AE Bladel
The Netherlands

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

Name: Genera Inc.
Address: 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 25 mg Tablets for dogs
Phenobarbital

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

Active substance per tablet
Phenobarbital 25 mg

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 to other barbiturates.
Do not use in animals with serious impaired hepatic function.
Do not use in animals with serious renal or cardiovascular disorders.
Do not use in dogs weighing less than 2.5 kg body weight.

6. ADVERSE REACTIONS

During start of therapy ataxia, sleepiness, lethargy and dizziness can very rarely occur but these effects are usually transitory and disappear in most, but not all, patients with continued medication.
Some animals can very rarely 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 very rarely 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 (occurring very rarely) as serum levels reach the higher ends of the therapeutic range.
High plasma concentrations may be associated with hepatotoxicity (very rare).
Phenobarbital can have deleterious effects on stem cells from bone marrow. Consequences are immunotoxic pancytopenia and/or neutropenia (very rare). 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, a decrease in the administered dose should be recommended.
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 inform your veterinary surgeon.
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7. TARGET SPECIES

Dogs.

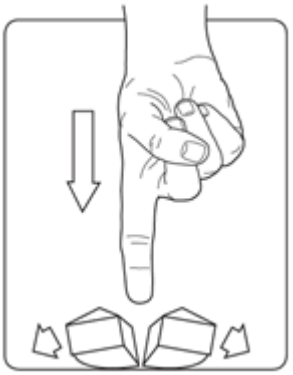
8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Administration route
For oral administration. 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. The required dosage will differ to some extent between individuals and with the nature and severity of the disorder

9. ADVICE ON CORRECT ADMINISTRATION

The crossed score line on one side of the tablet allows division into two (each part of 12.5 mg phenobarbital) or four (each part of 6.25 mg phenobarbital) equal parts.

- Place the tablet with the round side down on a flat surface
- Break the tablet into four equal parts by pressing on the top with your thumb or finger



The serum phenobarbital concentrations should be measured after steady state has been achieved. Blood samples could be taken at the same time to allow plasma phenobarbital concentration to be determined preferably during trough levels, shortly before the next dose of phenobarbital is due. 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 Tablets. However, if this cannot 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.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Do not store above 30oC.
Keep out of the reach and sight of children.
Keep the container in the outer package in order to protect from light.
Do not use after expiry date stated on the blister label and the carton.
Return any divided tablets to the opened blister pack and use within 48 hours.

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.

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:
Doses for smaller dogs cannot be adjusted in accordance with the recommended 20% regime, and therefore special care should be taken in monitoring these animals. Also see section 9.
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.
Caution is recommended in animals with impaired renal function, hypovolemia, anaemia and cardiac or respiratory dysfunction.
Before beginning the treatment monitoring of hepatic parameters should be performed.
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 can 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, so liver function tests are recommended. Increased liver enzyme values may not always require a dose reduction of phenobarbital if the serum bile acids are in the normal range.

In the light of isolated reports describing hepatotoxicity associated with combination anticonvulsant therapy, it is recommended that:
1. Hepatic function is evaluated prior to initiation of therapy (e.g. measurement of serum bile acids).
2. Therapeutic phenobarbital serum concentrations are monitored to enable the lowest effective dose to be used. Typically concentrations of 15-45µg/ml are effective in controlling epilepsy.
3. Hepatic function is re-evaluated on a regular (6 to 12 months) basis.
4. Seizure activity is re-evaluated on a regular basis.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Barbiturates can cause hypersensitivity. People with known hypersensitivity to barbiturates should avoid contact with the product.
Accidental ingestion may cause intoxication and could be fatal, particularly for children. Take utmost care that children do not come in contact with the product.
Phenobarbital is teratogenic and may be toxic to unborn and breastfeeding 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 accidental ingestion and prolonged skin contact with the product.
Keep this product in its original packaging to avoid accidental ingestion.
It is advisable to wear disposable gloves during administration of the product to reduce skin contact.

In case of accidental ingestion, seek medical attention immediately, advising medical services of barbiturate poisoning; 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.
Each time an unused part-tablet is stored until next use, it should be returned to the open blister space and inserted back into the cardboard box.
Wash hands thoroughly after use.

Pregnancy:
Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

Studies in laboratory animals have indicated that phenobarbital has an effect during prenatal growth, in particular causing permanent changes in neurological and sexual development. Neonatal bleeding tendencies have been associated with phenobarbital treatment during pregnancy.
Maternal epilepsy may be an additional risk factor for impaired foetal development. Therefore pregnancy should be avoided in epileptic dogs whenever possible. In case of pregnancy, 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. Discontinuation of treatment is not advised, but the dosage should be kept as low as possible.
Phenobarbital crosses the placenta and, at high doses, (reversible) withdrawal symptoms cannot be ruled out in new-borns.
The safety of the veterinary medicinal product has not been proven during pregnancy in dogs.

Lactation:
Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

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.
The safety of the veterinary medicinal product has not been proven during lactation in dogs.

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 α1acid 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 derivates, phenothiazines, antihistamines, clomipramine and chloramphenicol can increase 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.
Use of phenobarbital tablets in conjunction with primidone is not recommended as primidone is predominantly metabolized to phenobarbital.

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 and give respiratory and cardiovascular support as necessary.

The prime objectives of management are then 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 CNS stimulants (like doxapram) may stimulate the respiratory centre.

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)
100 tablets in a cardboard carton containing 10 aluminium/PVC blister strips each strip with 10 tablets.
100 tablets in a cardboard carton containing 10 aluminium/PVC/PE/PVdC blister strips each strip with 10 tablets.

500 tablets in a cardboard carton containing 50 aluminium/PVC blister strips each strip with 10 tablets.
500 tablets in a cardboard carton containing 50 aluminium/PVC/PE/PVdC blister strips each strip with 10 tablets.

Not all pack sizes may be marketed.

Approved 03 February 2023