ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE
{Cardboard box}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

PHENOVET 60 mg tablets for dogs
Phenobarbital

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains:

Phenobarbital 60 mg

3. PHARMACEUTICAL FORM

Tablet.

4. PACKAGE SIZE

60 tablets
180 tablets
300 tablets

5. TARGET SPECIES

Dogs.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Not applicable.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.
User warnings: People with known hypersensitivity to barbiturates should avoid contact with the veterinary medicinal product. Children are particularly at risk of intoxication which may prove fatal. Take utmost care that children do not come in contact with the product.

10. EXPIRY DATE

<EXP {month/year}>

11. SPECIAL STORAGE CONDITIONS

Keep the tablets in the original package. Any remaining portions of divided tablets should be replaced in the blister pocket, the blister strip should be returned to the cardboard box.

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.

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

Domes Pharma
3 rue André Citroën
63430 Pont-du Chateau
France

16. MARKETING AUTHORISATION NUMBER(S)

Vm 54982/4011

17. MANUFACTURER'S BATCH NUMBER

<Lot> {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

{Aluminium flat plate}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

PHENOVET 60 mg tablets for dogs
Phenobarbital

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Domes Pharma

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:
PHENOVET 60 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:
Domes Pharma
3 rue André Citroën
63430 Pont-du Chateau
France

Manufacturer responsible for batch release:
EUROPHARTECH
Rue Henri Matisse
63370 LEMPDES
FRANCE

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

PHENOVET 60 mg tablets for dogs
Phenobarbital

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

Each tablet contains:

Active substance:
Phenobarbital 60 mg

Oblong, white spotted tablet, with 3 scored lines.
The tablets can be divided into two or four equal parts.

4. INDICATION(S)

Prevention of seizures due to generalised epilepsy in dogs.

5. CONTRAINDICATIONS

Do not administer to animals with impaired hepatic function.
Do not use in animals with serious renal or cardiovascular disorders.
Do not use in dogs weighing less than 6 kg body weight.
Do not use in case of hypersensitivity to the active substance or to any other barbiturates or to any of the excipients.

6. ADVERSE REACTIONS

Occasionally polyphagia, polyuria and polydipsia have been reported, but these effects are usually transitory and disappear with continued medication.

Toxicity may develop at doses over 20 mg/kg/day or when serum phenobarbital levels rise above 45µg/ml.
At the start of therapy, ataxia and sedation 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. 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. Superficial necrolytic dermatitis may occur after administration of phenobarbital.
If adverse effects are severe, a decrease in the administered dose is 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.

7. TARGET SPECIES

Dogs.

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

For oral use.

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.

The required dosage will differ to some extent between individuals and with the nature and severity of the disorder.

Dogs should be dosed orally, starting with a dose of 2-5 mg per kg bodyweight per day. The dose should be divided and administered twice daily. The tablet can be divided into equal halves and quarters to provide 30 mg and 15 mg doses, respectively.

Tablets must be given at the same time each day to achieve successful therapy. The remaining tablet portion should be given at the next administration.

Steady state serum concentrations are not reached until 1-2 weeks after treatment is initiated. The full effect of the medication does not appear for two weeks and doses should not be increased during this time.

If seizures are not being controlled, the dosage may be increased by 20% at a time, with associated monitoring of serum phenobarbital levels. The phenobarbital serum concentration may be checked after steady state has been achieved, and if it is less

than 15 µg/ml the dose may be adjusted accordingly. If seizures recur the dose may be raised up to a maximum serum concentration of 45 µg/ml. High plasma concentrations may be associated with hepatotoxicity.
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.

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 (such as bromides) should be added to the treatment protocol.

Plasma concentrations should 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.

9. ADVICE ON CORRECT ADMINISTRATION

The remaining tablet portion should be given at the next administration.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Keep the tablets in the original package. Any remaining portions of divided tablets should be replaced in the blister pocket, the blister strip should be returned to the cardboard box.

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

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. Some dogs are free of epileptic seizures during the treatment, but some dogs show only a seizure reduction, and some dogs are considered to be non-responders.

Special precautions for use in animals:
In stabilised epileptic patients, it is not recommended to switch between phenobarbital formulations. 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.

Caution is recommended in animals with impaired renal function, hypovolemia, anemia 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 lactating women 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.

Use during pregnancy, lactation or lay:
Pregnancy:
Use only according 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 newborns.
The safety of the veterinary medicinal product has not been proven during pregnancy in dogs.

Lactation:
Use only according 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 newborns, 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 proteins, (such as α1acid glycoprotein, AGP), which bind drugs. Phenobarbital may reduce the activity of some drugs by increasing the rate of metabolism through induction of drug-metabolising enzymes in liver microsomes. Therefore special attention must be paid to the pharmacokinetics and doses of drugs simultaneously administered. The plasmatic concentration of a range of drugs (for example cyclosporine, thyroid hormones and theophylline) is decreased in the case of concurrent administration of phenobarbital. 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.
Cimetidine and ketoconazole are inhibitors of hepatic enzymes: concurrent use with phenobarbital can induce an increase of serum concentration of phenobarbital. Phenobarbital may decrease the absorption of griseofulvin. Concurrent use with potassium bromide increases the risk of pancreatitis. Use of phenobarbital tablets in conjunction with primidone is not recommended as primidone is predominantly metabolized to phenobarbital.
The following drugs can decrease the convulsive threshold: quinolones, high doses of β-lactam antibiotic, theophylline, aminophylline, 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, if appropriate, and give respiratory and cardiovascular support as necessary.

Management of overdose should consist of 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. Activated charcoal has been demonstrated to be of considerable benefit in enhancing the clearance of phenobarbital.

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

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

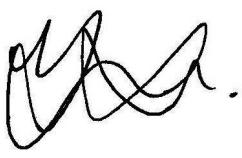
October 2022

15. OTHER INFORMATION

Packages size:
Cardboard box of 60 tablets.
Cardboard box of 180 tablets.
Cardboard box of 300 tablets.
Not all pack sizes may be marketed.

Marketing authorization number:
Vm 54982/4011

Classification of the medicinal product in terms of dispensing.
For animal treatment only.



Approved: 27 October 2022