

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE - CARTON

EPIPEN SOLUTION 4% w/v, oral drops

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

EPIPEN SOLUTION 4% w/v, oral drops

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Solution containing 4% w/v phenobarbital

3. PHARMACEUTICAL FORM

Oral drops

4. PACKAGE SIZE

30 ml

100 ml

250 ml

5. TARGET SPECIES

Dog

6. INDICATIONS

Read the package leaflet before use.

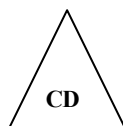
7. METHOD AND ROUTE OF ADMINISTRATION

Read package leaflet before use.

8. SPECIAL WARNINGS, IF NECESSARY

In the case of accidental ingestion, seek medical attention immediately advising medical services of barbiturate poisoning, or show this container. Keep away from sources of ignition. Do not smoke. Wash hands after use. Read the package leaflet before use.





Sch.3

9. EXPIRY DATE

EXP {month/year}>

10. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

Protect from light.

Store in tightly closed original container

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

Disposal: read the package leaflet.

12. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only.

POM-V

To be supplied only on veterinary prescription

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

Keep out of the sight and reach of children.

14. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vetoquinol UK Limited
Steadings Barn
Pury Hill Business Park
Nr. Alderton
Towcester
Northamptonshire
Northants
NN12 7LS

15. MARKETING AUTHORISATION NUMBER

Vm 08007/4081

16. MANUFACTURER'S BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE - LABEL

EPIPHEN SOLUTION 4% w/v, oral drops

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

EPIPHEN SOLUTION 4% w/v, oral drops

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Solution containing 4% w/v phenobarbital

3. PHARMACEUTICAL FORM

Oral drops

4. PACKAGE SIZE

30 ml

100 ml

250 ml

5. TARGET SPECIES

Dog

6. INDICATIONS

Read the package leaflet before use.

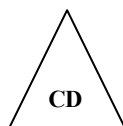
7. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.

8. SPECIAL WARNINGS, IF NECESSARY

In the case of accidental ingestion, seek medical attention immediately advising medical services of barbiturate poisoning, or show this container. Keep away from sources of ignition. Do not smoke. Wash hands after use. Read the package leaflet before use.





Sch.3

9. EXPIRY DATE

EXP {month/year}>

10. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

Protect from light.

Store in tightly closed original container

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

Disposal: read package leaflet.

12. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only.

POM-V

To be supplied only on veterinary prescription

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

Keep out of the sight and reach of children.

14. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vetoquinol UK Limited
Steadings Barn
Pury Hill Business Park
Nr. Alderton
Towcester
Northamptonshire
NN12 7LS

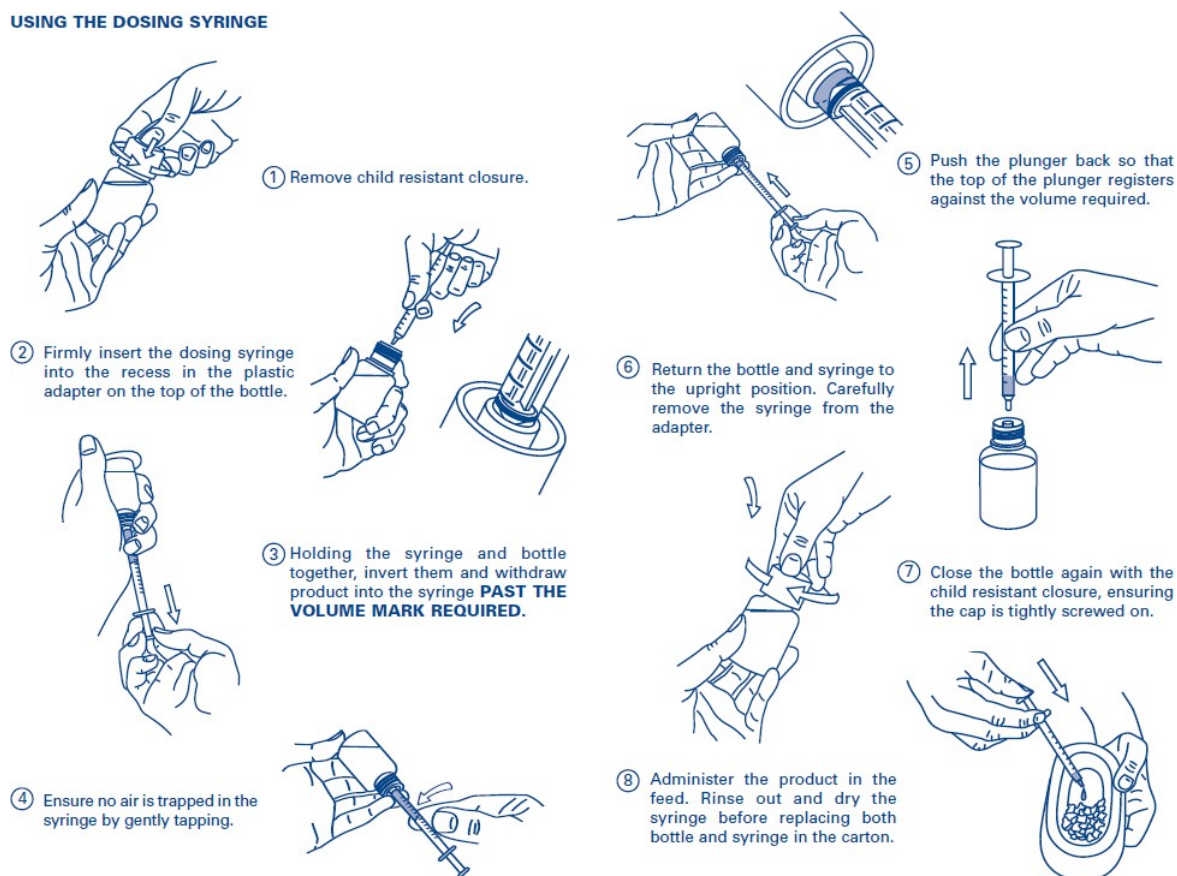
15. MARKETING AUTHORISATION NUMBER

Vm 08007/4081

16. MANUFACTURER'S BATCH NUMBER

Lot

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR:**EPIPEN SOLUTION 4% w/v, oral drops****USING THE DOSING SYRINGE**

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

Marketing authorisation holder
Vetoquinol UK Limited Steadings
Barn
Pury Hill Business Park Nr.
Alderton
Towcester
Northamptonshire
NN12 7LS

Site of batch release
VETOQUINOL SA
Magny-Vernois
70200 Lure France

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

EPIPHEN SOLUTION 4% w/v, oral drops
Phenobarbital

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

Oral solution containing 4% w/v phenobarbital

4. INDICATIONS

Phenobarbital is an antiepileptic agent for use in the control of epilepsy in the dog.

5. CONTRAINDICATIONS

Not for use in pregnant animals or nursing bitches.
Do not administer to animals with impaired hepatic function.
Do not use in cases of hypersensitivity to the active substance(s), to any other barbiturates or to any of the excipients
Do not use in animals with serious renal and/or cardiovascular/respiratory disorders.

6. ADVERSE REACTIONS

Ataxia, somnolence, listlessness and dizziness may occur rarely at the start of treatment. In some cases, these effects may persist for the entire duration of treatment.

A paradoxical hyperexcitability may occur rarely, particularly after first starting therapy. As this hyperexcitability is not linked to overdosage, no reduction of dosage is needed.

Sedation and ataxia may very rarely become significant concerns as serum levels reach the higher end of the therapeutic range.

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

Hepatotoxicity may develop very rarely at doses over 20mg/kg/day or when serum phenobarbital levels are high (see special precautions for use).

Phenobarbital can have deleterious effects on stem cells from bone marrow, immunotoxic pancytopenia and/or neutropenia and anaemia may occur very rarely.

Superficial necrolytic dermatitis may occur after administration of phenobarbital very rarely.

Hypoalbuminaemia was rarely reported. 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 (see special precautions for use).

In very rare cases, change of behaviour such as aggression was reported.

If adverse effects are severe, it is recommended to decrease the daily dose.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports)

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

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 - 5.0 mg/kg (0.06 - 0.125ml per kg) bodyweight per day. The dose should be divided and administered twice daily using the 2ml syringe provided. 1ml contains 40mg of phenobarbital.

DAILY DOSAGE GUIDE

The following doses should be divided and administered twice daily

Weight of dog	Volume of Epiphen Solution per day	Mg/kg
1-1.5 kg	0.1 ml	2.7 – 4.0
2-3 kg	0.2 ml	2.7 – 4.0
4-5 kg	0.4 ml	3.2 – 4.0
6-9 kg	0.6 ml	3.1 – 4.7
10 – 15 kg	1.2 ml	3.2 – 4.8
16-20 kg	1.6 ml	3.2 – 4.0

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 mg/l the dose may be adjusted accordingly. If seizures recur the dose may be raised up to a maximum serum concentration of 40 mg/l (see special precautions for use). High plasma concentrations may be associated with hepatotoxicity. Blood samples should 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.

9. ADVICE ON CORRECT ADMINISTRATION

10. WITHDRAWAL PERIOD

Not applicable

11. SPECIAL STORAGE PRECAUTIONS

Do not store above 25°C
Keep out of the sight and reach of children.
Protect from light.
Store in tightly closed original container.
Flammable liquid.

Do not use this veterinary medicinal product after the expiry date which is stated on the label and carton after EXP.

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.

To achieve successful therapy, administration of drops should occur at the same time(s) each day and should be co-ordinated with feeding times in a consistent manner.

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

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:

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 the minimum effective dose. 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.

Treating dogs with phenobarbital may lower 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. 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.

A wide therapeutic range of phenobarbital concentration in the serum of 15 mg/l to 40 mg/l is often stated. Optimal seizure control is achieved in most dogs with a serum phenobarbital concentration of between 25–30 mg/l. High serum concentrations of more than 35 mg/l should be avoided due to increased risk of hepatotoxicity. Below these ranges, in dogs with good seizure control, no change of dose may be necessary, as the concentration may be sufficient for that individual. As a general guide, serum phenobarbital concentration should be the lowest to achieve a decrease in seizure frequency of greater than 50%, or absence of seizures where possible, without intolerable side effects.

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

Flammable, keep away from sources of ignition. Do not smoke.

People with known hypersensitivity to phenobarbital or other barbiturates should avoid contact with this veterinary medicinal product.

It is advisable to wear disposable gloves when handling the product, to reduce skin contact.

Phenobarbital is a teratogen and developmental neurotoxicant and transfers to breast milk.

The product should not be administered by pregnant women, women intending to become pregnant or whose pregnancy status is unknown, as well as lactating women.

Ingestion of Phenobarbital can cause neurotoxicity which may prove fatal. Take utmost care that children do not come into any contact with the product. Children are particularly at risk of intoxication. To prevent accidental ingestion of

phenobarbital, the vial should be closed immediately after withdrawing the required number of drops for one administration. The vial should be stored in a safe place out of the sight and reach of children.

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.

Wash hands after use.

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.

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:

Phenobarbital may reduce the activity of some drugs by increasing the rate of metabolism through induction of drug-metabolising enzymes in liver microsomes.

A therapeutic dose of phenobarbital for antiepileptic therapy can significantly induce plasma protein (such as α_1 acid 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.

Concurrent use with potassium bromide increases the risk of pancreatitis.
Concurrent use with other drugs having a central depressive effect can result in an increase of the effect of central depressive drugs.

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 blood concentration of griseofulvin by reducing its absorption and/or inducing hepatic microsomal enzymes.

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.

Use of phenobarbital in conjunction with primidone is not recommended as primidone is predominantly metabolised to phenobarbital.

Overdose (symptoms, emergency procedures, antidotes):

Overdosage may result in coma, severe respiratory and cardiovascular depression, hypotension and shock leading to renal failure and death.

Following the recent ingestion of an overdose, the stomach may be emptied by lavage.

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.

Incompatibilities:

None known

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

Any unused product must be destroyed in accordance with the Misuse of Drugs Regulations (2001). Any waste material should be disposed of in accordance with local requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

December 2022

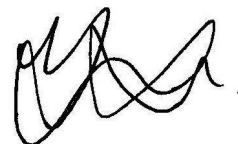
15. OTHER INFORMATION

PHARMACOLOGICAL

PROPERTIES:

The antiepileptic effects of phenobarbital are probably the result of at least two mechanisms:- Decreased monosynaptic transmission, which presumably results in reduced neuronal excitability and an increase in the motor cortex's threshold for electrical stimulation. 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%. About 45% of the plasma concentration is protein bound. Metabolism is by aromatic hydroxylation of the phenyl group in the para position, and about one third of the drug is excreted unchanged in the urine. Elimination half-lives vary considerably between individuals and range from about 40 - 90 hours.

Not all pack sizes may be marketed.



Approved: 05 January 2023