ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

Revised: May 2024
AN: 04032/2022

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

{Cardboard box}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Soliphen 120 mg tablets

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains:
Phenobarbital…….. 120 mg

3. PACKAGE SIZE

60 tablets
96 tablets

4. TARGET SPECIES

Dogs (weighing at least 12 kg)

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Oral use

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp. {mm/yyyy}

9. SPECIAL STORAGE PRECAUTIONS

Store 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. Remaining tablet portions should be given at the next administration.

10. THE WORDS “READ THE PACKAGE LEAFLET BEFORE USE”

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

DOMES PHARMA

14. MARKETING AUTHORISATION NUMBERS

Vm 54982/3001

15. BATCH NUMBER

Lot {number}

Revised: May 2024
AN: 04032/2022

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{Blister}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Soliphen

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

120 mg

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Soliphen 120 mg tablets for dogs

2. Composition

Each tablet contains:

Active substance:
Phenobarbital…….. 120 mg

Oblong, white spotted tablet, with three scored lines (both sides).
The tablets can be divided into two or four equal parts.

3. Target species

Dogs (weighing at least 12 kg)

4. Indications for use

Prevention of seizures due to generalised epilepsy.

5. Contraindications

Do not administer to animals with seriously impaired hepatic function.
Do not use in animals with serious renal or cardiovascular disorders.
Do not use in dogs weighing less than 12 kg body weight.
Do not use in cases of hypersensitivity to the active substance or to any other barbiturates or to any of the excipients.

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.
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.
Therapeutic phenobarbital serum concentrations should be monitored to enable the lowest effective dose to be used. Typically, concentrations of 15-40 µg/ml are effective in controlling epilepsy.
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 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.

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 stabilised epileptic patients, it is not recommended to switch from other phenobarbital formulations to the veterinary medicinal product. 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.
The tablets are flavoured. In order to avoid any accidental ingestion, store tablets out of reach of the animals.

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 veterinary medicinal 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 veterinary medicinal product. Keep this product in its original packaging to avoid accidental ingestion. 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.
Phenobarbital is teratogenic and may be toxic to unborn and breastfed 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.
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.
Wash hands thoroughly after use.

Pregnancy:
Laboratory studies in 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.

Lactation:
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.

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Use only according 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 proteins, (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, 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 tablets in conjunction with primidone is not recommended as primidone is predominantly metabolized to phenobarbital.

Overdose:
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.

7. Adverse events

Dogs:
Rare (1 to 10 animals / 10 000 animals treated):
Diarrhoea, emesis
Ataxia[1,2,3]
Very rare (<1 animal / 10 000 animals treated, including isolated reports):
Polyphagia[1], polydipsia[1]
Polyuria[1]
Sedation[1,2,3]
Hyperexcitability (paradoxical)[2,4]
Pancytopenia[5] (immunotoxic), neutropenia[5]
Hepatic toxicosis[6]
Low thyroxine (T4)[7], Low free thyroxine (FT4)[7]

[1]effects usually transitory, which disappear with continued medication in most patients.
[2]at the start of therapy.
[3]become significant concerns as serum levels reach the higher ends of the therapeutic range.
[4]not linked to overdosage, so no reduction of dosage is needed.
[5]can result from deleterious effects of phenobarbital on bone marrow stem cells. Disappear after the treatment's withdrawal.
[6]may be due to high plasma concentrations.
[7]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 is recommended. Toxicity may develop at doses over 20 mg/kg/day or when serum phenobarbital levels rise above 45µg/ml.

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 either 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:
Website: *https://www.gov.uk/report-veterinary-medicine -problem/animal-reacts-medicine*
e-mail: adverse.events@vmd.gov.uk

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

Oral use.
For the decision to start antiepileptic drug therapy, see section 6.
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 two or four equal parts to provide 60 mg and 30 mg doses, respectively.
Tablets must be given at the same time each day to achieve successful therapy.
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.
Any adjustments to the starting dose are best made on the basis of clinical efficacy, blood concentrations of phenobarbital and the occurrence of undesired effects.
Due to differences in the excretion of phenobarbital and differences in sensitivity the final effective doses may vary considerably between patients (from 1 mg to 15 mg/kg body weight twice a day).
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

None.

10. Withdrawal periods

Not applicable.

11. Special storage precautions

Keep out of the sight and reach of children.
Store 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. Remaining tablet portions should be given at the next administration.

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

Marketing authorisation numbers:
Vm 54982/3001

Pack sizes:
Cardboard box containing 5 or 8 PVC/aluminium thermosealed blisters of 12 tablets.
Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

November 2023

Detailed information on this veterinary medicinal product is available in the Union Product Database
(https://medicines.health.europa.eu/veterinary).

16. Contact details

Marketing authorisation holder:
DOMES PHARMA
3 rue André Citroën
63430 Pont-du-Château
France

Manufacturer responsible for batch release:
EUROPHARTECH
34 rue Henri Matisse
63370 Lempdes
France

Local representatives and contact details to report suspected adverse reactions:
For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

TVM UK ANIMAL HEALTH LTD Building B, Kirtlington Business Centre, Kirtlington OX5 3JA United Kingdom Tel 0800 038 5868 Email: help@tvm-uk.com

17. Other information

[For MRP/DCP/SRP and national procedures: To be completed nationally.]"

Approved: 11 May 2024