Vetoquinol UK Ltd

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Epiphen 30 mg and 60 mg Tablets

Species: Dogs

Therapeutic indication:Pharmaceuticals: Neurological preparations: Others

Active ingredient: Phenobarbital

Product: Epiphen 30 mg and 60 mg Tablets

Product index: Epiphen Tablets

Incorporating:

Presentation

Tablets for oral administration.

Phenobarbital tablets are available in two strengths:

White, circular biconvex tablets plain on both sides containing 30 mg phenobarbital.

White, circular biconvex tablet with stamp '60' on surface, containing 60mg phenobarbital.

Uses

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

Dosage and administration

Amounts to be administered and administration route

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 2-5mg per kg bodyweight per day. The dose should be divided and administered twice daily.

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 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.

Epiphen 30mg tablets

For accuracy of dosing, dogs under 6kg should commence therapy with Epiphen Solution. Tablets are not intended to be subdivided.

Epiphen 60mg tablets

For accuracy of dosing, dogs under 6 kg should commence therapy with Epiphen solution, and dogs between 6 and 12 kg should commence therapy with either Epiphen solution or Epiphen 30mg tablets.

Tablets are not intended to be subdivided.

Contra-indications, warnings, etc

Contra-indications

Not for use in pregnant animals.

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.

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 tablets 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 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.

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

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 tablets, the container should be closed immediately after withdrawing the required number of tablets for one administration. Part tablets should be placed back into the container and used at the next administration, as even part tablets pose a health risk to small children if ingested. The container 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.

Adverse Reactions (frequency and seriousness)

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)

Use during pregnancy or lactation

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 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.

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 metabolized to Phenobarbital.

Overdose (symptoms, emergency procedures, antidotes), if necessary

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.

Withdrawal period

Not applicable

Pharmaceutical precautions

Do not store above 25°C. Protect from light. Store in a dry place and replace the closure promptly.

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.

NOAH Compendium

Legal category

Legal category:POM-V

Legal category description:CD(Sch 3)

Packaging quantities

White, circular, biconvex tablets (30mg 5.5mm diameter, 60mg 6.5mm diameter) for oral administration packed in polypropylene (PP) tubes with low density polyethylene (LDPE) caps or high density polyethylene (HDPE) jar securitainer and polypropylene (PP) lid containing a desiccant (silica gel).

Pack size: 1,000 tablets.

Printed outer carton also containing a product leaflet.

Further 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.

Shelf Life

Shelf life of the veterinary medicinal product as packaged for sale: 5 years

Marketing Authorisation Number

Epiphen 60 mg tablets, UK (GB): Vm 08007/5017

Epiphen 60 mg tablets, UK (NI): Vm 06462/3008

Epiphen 30 mg tablets, UK (GB): Vm 08007/5016

Epiphen 30 mg tablets, UK (NI): Vm 06462/3007

Significant changes

GTIN

GTIN description: Epiphen 30mg tablet

GTIN:03605874237575

NOAH Compendium

GTIN description: Epiphen 60mg tablet

GTIN:03605874237629