SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Phenotab Flavoured 25 mg Tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substance:

Phenobarbital 25 mg

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White, speckled with brown spots, round and convex tablet with a cross-shaped break line on one side.

Tablets can be divided into 2 or 4 equal parts.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

Prevention of seizures due to generalised epilepsy.

4.3 Contraindications

Do not use in known cases of hypersensitivity to the active substance, any of the excipients or other barbiturates. Do not use in animals with severe liver disease.
Do not use in animals with serious renal or cardiovascular disorders.

4.4 Special warnings for each target species

It is recommended that the clinical pathology of the patient is monitored, the first time 2-3 weeks after initiation of therapy and subsequently every 4-6 months. It is important to know that the effects of hypoxia can cause increased levels of hepatic enzymes after a seizure.
Long-term therapy with phenobarbital results in habituation and dependence, which can lead to a spontaneous return of symptoms upon sudden discontinuation of therapy.
To achieve successful therapy, administration of tablets at the same time each day is essential.

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.

4.5 Special precautions for use

Special precautions for use in animals

Caution is required in animals with impaired liver and / or renal function, hypovolaemia, anemia and cardiac or respiratory dysfunction.

It is recommended to evaluate hepatic function prior to initiation of the therapy. The chance of hepatotoxic side effects can be diminished or delayed using an effective dose that is low as possible.

Phenobarbital may increase the activity of serum alkaline phosphatase and transaminases. These may demonstrate non-pathological changes, but an increase in the activity of serum alkaline phosphatase and transaminases could also represent hepatotoxicity. Therefore, in the case of suspected hepatotoxicity, liver function tests are recommended.

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 stabilized epileptic patients, caution should be taken when switching between phenobarbital formulations.

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 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. 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. In case of accidental ingestion, seek medical attention immediately and show the package leaflet or the label to the physician.

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 women who are breastfeeding should avoid accidental ingestion due to hand-to-mouth contact and prolonged skin contact with the product.

It is advisable to wear disposable gloves during administration of the product to reduce skin contact with the product.
Wash hands thoroughly after use.

4.6 Adverse reactions (frequency and seriousness)

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.
If adverse effects are severe, a decrease in the administered dose is recommended.

4.7 Use during pregnancy and 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.
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.

4.8 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 (e.g. antiepileptics, chloramphenicol, corticosteroids, doxycycline, beta blockers and metronidazole) 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.

4.9 Amounts to be administered and administration route

Oral use

Dosage
The recommended starting dose is 2.5 mg phenobarbital per kg body weight (equivalent to 1 tablet per 10 kg), administered twice daily.
Due to the cross-shaped score line, the tablets can be divided into two equal halves (12.5 mg phenobarbital) or four equal quarters (6.25 mg phenobarbital). Divided tablets should be used at the next administration.

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.
Determining blood levels is essential for a correct therapy. The phenobarbital levels considered therapeutically effective vary from 15 to 40 µg/ml.
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).
In case of insufficient therapeutic efficacy, the dosage can be increased in steps of 20% at a time, with associated monitoring of serum phenobarbital levels.

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 always 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.

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

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.

4.11 Withdrawal period

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antiepileptics / barbiturates and derivatives
ATCvet code: QN03AA02

5.1 Pharmacodynamic properties

Phenobarbital is a barbiturate with an anti-epileptic effect. Phenobarbital is used in the ideopathic form of generalized epilepsy in dogs. Phenobarbital operates at the central level, affects the system of the inhibitory neurotransmitter gamma-aminobutyric acid, and in this way inhibits convulsions. The more specific action of phenobarbital, compared with other barbiturates, against epilepsy could be related to its pKa (7.3). The local acidosis in an affected/active neuronal area will cause the transformation of more phenobarbital into its active form.
Barbiturates cause enzyme induction and thereby accelerate their own degradation.

5.2 Pharmacokinetic particulars

As a weak acid, phenobarbital is absorbed well from the gastrointestinal tract following oral administration to dogs, although peak plasma concentrations are not achieved until 1.5-6 hours after administration. Plasma protein binding of phenobarbital is 45% and the distribution volume is 0.7 ± 0.15 l/kg. A steady-state serum concentration is achieved 8-15.5 days after treatment is initiated. Phenobarbital is reasonably fat-soluble and crosses the blood-brain barrier slowly. The barbiturate effect therefore develops slowly, but persists for a long period of time. Due to the moderate fat solubility of phenobarbital redistribution to the adipose tissue occurs slowly. Phenobarbital crosses the placental barrier and enters breast milk.

Phenobarbital is converted in the liver into p-hydroxy-phenobarbital, which, due to a lower antiepileptic effect, does no longer significantly contribute to the phenobarbital action. From the dose administered approximately 25% is excreted unchanged in the urine (elimination half-life 37-75 hours) and about 75% as glucuronide and sulphate derivatives of p-hydroxyphenobarbital and as p-hydroxyphenobarbital itself.
After a daily administration of 5.5 mg phenobarbital per kg body weight for 90 days a lower elimination half-life is observed (from 88.7 ± 19.6 to 47.5 ± 10.7 hours).
Under alkaline conditions urinary excretion of phenobarbital is accelerated.
There is wide individual variation in the degree of phenobarbital metabolism due to the effect of phenobarbital on microsomal liver enzymes.
Elimination half-lives vary not only between animals but also within one and the same animal.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Lactose monohydrate
Sodium starch glycolate (Type A)
Silica, colloidal hydrated
Magnesium stearate
Yeast (dried)
Chicken flavour

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 30 months.

6.4 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.
Keep the blister in the outer carton.
Any remaining portions of divided tablets should be returned in the opened blister and given at the next administration.

6.5 Nature and composition of immediate packaging

Aluminium - PVC/PE/PVDC blister

Package sizes:
Cardboard box with 3 blisters of 10 tablets
Cardboard box with 5 blisters of 10 tablets
Cardboard box with 10 blisters of 10 tablets
Cardboard box with 25 blisters of 10 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

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

7. MARKETING AUTHORISATION HOLDER

CP-Pharma Handelsgesellschaft mbH
Ostlandring 13
31303 Burgdorf
Germany

8. MARKETING AUTHORISATION NUMBER

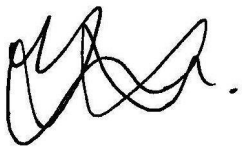
Vm 20916/4032

9. DATE OF FIRST AUTHORISATION

25 August 2020

10. DATE OF REVISION OF THE TEXT

August 2020



Approved: 25 August 2020