ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Phenoleptil 12.5 mg Tablets for dogs

Updated: February 2018

PuAR correct as of 02/04/2019 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0336/001/DC
Name, strength and pharmaceutical form	Phenoleptil 12.5 mg Tablets for dogs
Applicant	LeVet Pharma B.V.
Active substance(s)	Phenobarbital
ATC Vetcode	QN03AA02
Target species	Dog
Indication for use	Prevention of seizures due to generalised epilepsy in dogs.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 13(3) of Directive 2001/82/EC, as amended by 2004/28/EC.
Date of completion of the original decentralised procedure	04 March 2010
Concerned Member States for original procedure	France Germany Italy Spain
Concerned Member States added following Repeat Use Authorisation.	Austria, Belgium, Czech Republic, Denmark, Finland, Greece, Hungary, Iceland, Ireland, Luxembourg, Norway, Poland, Portugal, Slovakia, Sweden

I. SCIENTIFIC OVERVIEW

Phenoleptil 12.5 mg tablets for dogs is authorised for use in dogs for the prevention of seizures due to generalised epilepsy. Each tablet contains 12.5 mg phenobarbital as an active substance. The dosage rate of phenobarbital is 2.5 mg per kg body weight twice daily. However, due to differences in phenobarbital excretion and differences in sensitivity among patients the active doses may vary considerably, ranging from 1 mg to 15 mg per kg bodyweight twice daily. Do not use in dogs weighing less than 5 kg bodyweight. Refer to the SPC for information on the adjustment of dose for small dogs and for information on switchability between different phenobarbital-containing products.

The application was made in accordance with article 13(3) of Directive 2001/82/EC, as amended by 2004/28/EC i.e. hybrid application. Bioequivalence is claimed with the reference products, Epiphen 30 mg Tablets and Epiphen 60 mg tablets, which have been authorised in the UK since April 1996.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species; the possible reactions are indicated in the SPC. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in

the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains phenobarbital as an active substance and lactose monohydrate, microcrystalline cellulose, pig liver flavour, dried yeast from *Saccharomyces,* sodium starch glycolate (Type A), silica colloidal anhydrous and magnesium stearate as excipients.

The product is packaged in aluminium /PVC strips. Each strip contains 10 tablets and is supplied in cardboard boxes with 5, 10, 25, 50 or 100 strips.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The supporting data for phenobarbital have been provided in the form of a EDQM[1] Certificate of Suitability. It is considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified.

There are six excipients used in the formulation and each has been used previously in veterinary medicines. Lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, silica colloidal anhydrous and magnesium stearate have monographs in the Ph. Eur. and each comply with the requirements of the current edition of the Ph. Eur.

The applicant provided raw material specification for dry beef flavour 201627, comprising tests of appearance, identity and loss on drying. This is considered acceptable.

[1] The European Directorate for the Quality of Medicines & HealthCare.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

The magnesium stearate is a material that could be sourced from either animal or non animal sources. A declaration has been provided certifying that the raw materials, ingredients and additives used to produce magnesium stearate are exclusively of synthetic and vegetable origin.

E. Control on intermediate products

Not applicable.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. The satisfactory validation data for the analytical methods have been provided.

G. Stability

Stability data on the active substance have been provided for twelve batches of phenobarbital. Based on the data provided, a retest interval of five years was justified.
Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life. The shelf-life of the veterinary medicinal product as packaged for sale is 3 years.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Special precautions for storage:
Keep the container in the outer package in order to protect from light.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has submitted a number of published references to support the pharmacology of phenobarbital. This is discussed under section IV.

Toxicological Studies

The applicant has submitted a number of published references which describes that the toxicity of phenobarbital is well established and extensively reported.

Single dose toxicity

The applicant has submitted a number of published references of single dose toxicity derived from RTECS[2] Summary of Phenobarbital Sodium which reports LD_{50} values in the ranges from 40-226 mg/kg body weight for intravenous administration, 123-152 mg/kg body weight for intraperitoneal administration and 150-200 mg/kg body weight for oral administration. The lowest published toxic dose in man is reported as 36 mg/kg, equivalent to approximately 2 g for a 60 kg man.

Repeated dose toxicity

The applicant has submitted a number of published references of repeat dose toxicity data derived from RTECS Summary of Phenobarbital Sodium which describes the studies conducted in laboratory animals and reports adverse effects, mainly hepatic and biochemical or blood changes. The LOELs[3] reported were 70 mg/kg to 2100 mg/mg.

Reproductive toxicity

Studies of the effects on reproduction:

The applicant has submitted 3 references which describe that treatment during prenatal development can produce permanent alterations in sexual maturation and that phenobarbital may lead to sexual dysfunction in later life. Results reported that concentrations of phenobarbital in the plasma is not an appropriate indicator of the dynamics of the substance and must be used cautiously during pregnancy and at a minimum therapeutic dose.

Embryotoxicity/foetotoxicity:

The applicant has submitted a number of references of embryotoxicity and teratogenicity data which describes that phenobarbital is a teratogen and developmental neurotoxicant in humans and experimental animals. Exposure of rats in *utero* induces long-term effects on hepatic drug-metabolizing enzymes. Neuroendocrine effects on reproductive function have been noted in exposed adult male rats and female hamsters.

[2] Registry of Toxic Effects of Chemical Substances
[3] Lowest Observed Effect Levels

Mutagenicity:
The applicant has submitted 8 references of mutagenicity data derived from RTECS Summary of Phenobarbital Sodium which indicated that phenobarbital is not genotoxic.

Carcinogenicity:
The applicant has submitted 3 references which indicated that phenobarbitone is widely reported as a tumour promoter for mouse and rat liver when administered after hepatocarcinogens. It also induces rodent liver tumours in laboratory studies after 1-2 years. The development of these tumours is usually towards the end of the life span of the rodents. An *in vitro* study suggested that a fraction of the hepatocyte population in aging mice are more highly susceptible to phenobarbital carcinogenesis than hepatocytes from younger mice. Phenobarbitone has been shown to enhance the development of pre-neoplastic lesions in rat liver, and it is suggested that the carcinogenicity of phenobarbitone occurs by a mechanism of promotion exerted on pre-existing abnormal liver cells that give rise to the "spontaneously" occuring liver lesions and neoplasms in old rodents. Detailed epidemiological studies on humans using phenobarbitone have not revealed evidence of carcinogenicity.

Other Studies

Special studies:
The applicant has submitted 2 references which describes hypersensitivity in humans. Phenobarbital induces hepatic microsomal enzyme activity and can therefore alter the metabolism of any drug which undergoes metabolism by this route. The toxicity of these drugs can be enhanced by the increased activity accumulating toxic metabolites quicker than they can be eliminated and so contributing to the hepatotoxicity that can occur with chronic anticonvulsant therapy. The increase in activity can be used therapeutically as it can increase the elimination of body constituents such as bilirubin and reduce hyperbilirubinaemia in neonatal jaundice.

Observations in Humans

The applicant has submitted a number of references of observations in humans reporting the side effects and adverse effects of treatment with phenobarbital. Phenobarbital was the first synthetic drug to be introduced for the treatment of human epilepsy in 1912 and is now the only barbiturate used as an anti-epileptic drug. It is used to control tonic-clonic and partial seizures and the dose is adjusted to the needs of the individual patient to achieve adequate control. Care is required when withdrawing phenobarbital therapy in epileptic patients, to avoid precipitating an increase in seizures.

The most frequent adverse effect following administration of phenobarbital is sedation, but this often becomes less marked with continued administration. Prolonged administration may occasionally result in foliate deficiency or hypocalcaemia, and there have been rare reports of megaloblastic anaemia and osteomalacia. Hypersensitivity reactions occur in a small proportion of patients and there have been reports of hepatitis and disturbances in liver function.

Paradoxical excitement, irritability and hyperexcitability may sometimes occur, particularly in children and the elderly.

Microbiological Studies
Phenobarbital is not known to have antimicrobial activity.

User Safety
The following operator warnings are included in the SPC and product literature:

- People with known hypersensitivity to barbiturates should avoid contact with the veterinary medicinal product. Wash hands after use.
- In case of accidental ingestion seek medical advice immediately and show the package leaflet or the label to the doctor.

Ecotoxicity
The applicant has provided a first phase environmental risk assessment in compliance with the relevant guideline.

The assessment ended at Phase I as the products will only be used in dogs and exposure of the environment is not sufficient to require further assessment. The warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies
The active substance, phenobarbital has a well-established use in the treatment of idiopathic epilepsy in dogs. The applicant has demonstrated the mode of action adequately through bibliographical references. They have also demonstrated the various secondary pharmacodynamic effects which explain the known side effects of dosing with this active substance. Bioequivalence is claimed with the reference product which have been authorised in the UK since 1996.

Pharmacology
Pharmacodynamics
Pathophysiology of seizures:
The applicant has provided bibliographic data to explain the pathophysiology of seizures. Neuronal cells have a normal RMP[4] of -70 mV and this is maintained by the Na^+-K^+-adenosine triphosphatase (ATPase) pump. If the RMP becomes sufficiently positive it can reach the threshold and then an action potential is generated along the neuron. It is depolarised. Inappropriate depolarization may occur due to alterations of the Na^+ - K^+ pump; permeability changes in the cell membranes such as induced by hypoxia, inflammation, or trauma; altered

[4] Resting Membrane Potential

concentrations of excitatory (increased) or inhibitory (decreased) neurons; or altered cellular metabolism. Seizures are the clinical result of rapid, excessive neuronal discharge in the brain. Once initiated, the seizure discharge may synchronise with other neurons and propagate to surrounding areas in the brain.

Mode of action of phenobarbital:
Phenobarbital decreases seizure activity by enhancing the responsiveness to the inhibitory postsynaptic effects of γ-amino butyric acid (GABA). This opens chloride channels resulting in higher intracellular concentrations of chloride and hyperpolarisation of the RMP. In addition, phenobarbital inhibits glutamate activity and may target ion fluxes such as decreasing sodium or calcium influx. By these mechanisms, phenobarbital both increases the seizure threshold required for seizure discharge and decreases the spread of discharge to surrounding neurons.

Secondary pharmacodynamic effects:
Phenobarbital is reported to cause non-pathological changes in hepatic clinical laboratory tests due to enzyme induction. This is especially for mixed-function oxidase induction and appears to be dose related. In the dog, phenobarbital increases clonazepam clearance due to the enzyme induction caused by phenobarbital. Prolonged administration of phenobarbital (180 mg/kg/day orally) decreased bioavailability of propanolol and altered the binding, metabolism and the pharmacokinetics of propanolol. Phenobarbital at a dose of 16 mg/kg/day for 14 days, reduced the area under the plasma concentration curve and anaesthesia time in greyhounds anaesthetised with thiopental. There is evidence that enzyme induction can increase the formation of drug from prodrug, and it may promote the effects of tumour forming substance.
Phenobarbital is reported to induce α1acid glycoprotein (AGP)[5]. This is dose dependant and has been shown in treated epileptic dogs. As phenobarbital alters plasma AGP concentrations the pharmacokinetics of drugs which bind to AGP will be affected. This is likely to affect efficacy and safety of other drugs. The published literature also provided evidence of several drug interactions with phenobarbital.

Pharmacokinetics:
The applicant has submitted bibliographic data to support the pharmacokinectics of phenobarbital in dogs.

Absorption:
Phenobarbital is a weak acid and therefore it is absorbed well after oral administration. It is almost completely bioavailable and bioavailability is between 86% to 96%. T_{max} is around 4 to 6 hours post administration. Food has little effect on the rate of absorption (C_{max}) of a tablet formulation of phenobarbital but decrease the extent of absorption (AUC) by around 10 %.

Distribution:
Phenobarbital is lipid soluble but less than some anticonvulsants and can take as long as 15 minutes to distribute into the Central Nervous System (CNS) to

[5] Main binding protein for basic drugs in plasma

achieve therapeutic levels. It has a large volume of distribution. The volume of distribution tended to increase with dose. Phenobarbital is less than 50% protein bound. Phenobarbital is also distributed to saliva (pH and volume dependent) and hair (possibly melanin dependent).

Metabolism:
Phenobarbital is metabolised slowly through microsomal enzyme action by oxidative hydroxylation to form hydroxyphenobarbital. This metabolite has weak anticonvulsant activity and does not contribute significantly to the action of phenobarbital. In the dog hydroxyphenobarbital is rapidly eliminated from the blood by conjugation with glucuronide and excretion in the urine.

Elimination:
Elimination half-lives vary considerably between individuals and range from about 40-90 hours.

The applicant also conducted a study to obtain information concerning the pharmacokinetics of phenobarbital, during and following the repeated oral administration of the test item to healthy dogs. It was a parallel, multidose GLP[6] study. A suitable number of dogs were used in the study. The test product was administered orally at 2.5 mg/kg bodyweight twice daily for seven days. The tablets were not administered with food and food was offered four hours after dosing. Basic health parameters, clinical examinations were monitored at intervals throughout the study. From day 0 administration of the test product was started and blood samples were taken at regular intervals. Phenobarbital concentrations were determined from the plasma of blood samples by a validated method. The study concluded that the test product was well-tolerated in the study. Phenobarbital was absorbed fairly rapidly from this tablet formulation but eliminated slowly and therefore accumulation occurred with time to a steady state. This is considered acceptable.

Tolerance in the Target Species of Animals

The applicant has submitted bibliographic data to support the target species tolerance which showed that phenobarbital is well tolerated at therapeutic serum concentrations in the dog. The side effects of phenobarbital are known and the excipients used in the product are commonly used in veterinary tablet formulations. Phenobarbital has a narrow margin of safety and this varies with each individual dog. Therefore, treatment with this product has to be monitored closely by the clinician and adjusted according to serum phenobarbital concentration level.

Resistance

No data have been submitted. This is considered acceptable.

[6] Good Laboratory Practice

IV.B Clinical Studies

The applicant has submitted five references to support the clinical efficacy of phenobarbital. The first literature reference described the relative efficacies of primidone, phenobarbital and phenytoin. The correlations between drug dosage, serum drug concentrations, and efficacy for each of the three anticonvulsants was tested. The study was conducted on a suitable number of dogs. From the study, it was concluded that 60% of dogs which had adequate serum concentrations of active substance had their seizures controlled. Seizure control correlates better with serum concentration of phenobarbital than with dose of phenobarbital. A starting dose of 5 mg/kg per day divided into two doses and given orally was recommended. If the trough serum level was < 15 µg/ml after two weeks of treatment then the dose should be increased.

The second literature reference described a study of epileptic dogs in order to evaluate epilepsy in dogs as a model for epilepsy in humans, in particular clinical and electroencephalographic observations. This study supported the efficacy of phenobarbitone in seizure control in dogs with epilepsy.

The third literature reference described a randomised, positively controlled study to determine whether primidone had any advantage over phenobarbital in the treatment of generalised tonic-clonic seizures, or whether primidone acts only via the metabolite phenobarbital. The inclusion criterion was for dogs with generalised tonic-clonic seizures but without progressive brain disease. A suitable number of dogs were divided into different treatment groups. One group was treated with phenobarbital and other group was treated with primidone. The dogs in either group were treated according to clinical requirement based on plasma concentrations and clinical signs. It was concluded that primidone had greater hepatotoxicity based on more raised liver enzymes. However, this may not be entirely correct as this may indicate more enzyme induction.

The fourth literature reference described a clinical and epidemiological study with the purpose of defining environmental factors that may trigger seizures in dogs with idiopathic epilepsy; of analysing clinical characteristics of seizures in Labrador Retrievers and of analysing possible explanations for differences in the long term course of disease despite identical treatment conditions. The study supported the use of phenobarbital to treat idiopathic epilepsy in Labrador Retrievers starting with a dose of approximately 2.5 mg/kg twice daily and increasing it to achieve clinical improvement and a target serum phenobarbital level.

The fifth literature reference described an experimental and exploratory clinical trial in dogs with epilepsy concerning the anticonvulsant efficacy of the low affinity partial benzodiazepine receptor agonist, ELB 138. This study supported the efficacy of the active substance.

In order to demonstrate bioequivalence with the reference product, a study was conducted to obtain the dissolution profiles of phenoleptil tablets compared to the reference products. The dissolution profiles of the phenoleptil 12.5 mg and the 50 mg tablets and of the reference products were studied at different pH

values. The number of tablets used per dissolution tank depended on the tablet strength. Phenobarbital concentrations were determined by means of a validated method. The study demonstrated more rapid, but comparable, dissolution of the phenoleptil tablets than the reference product. All excipients except beef flavour are considered as standard excipients in tablet manufacturing and not suspected of having any impact on the solubility of the active substance.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)