Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Lepitil 60 mg Flavoured Tablets for Dogs

Lepitil vet 60 mg Tablets for Dogs
(SE)

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0438/001/DC
Name, strength and pharmaceutical form	Lepitil 60 mg Flavoured Tablets for Dogs
Applicant	Channelle Pharmaceuticals Manufacturing Ltd Loughrea Co Gallaway Ireland
Active substance(s)	Phenobarbital
ATC Vetcode	QN03AA02
Target species	Dog
Indication for use	Phenobarbital is an antiepileptic agent for the 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	Generic hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	24th April 2013
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Germany, Sweden

I. SCIENTIFIC OVERVIEW

Lepitil 60 mg Flavoured Tablets for Dogs is a generic hybrid based on the reference product Epiphen 60 mg Tablets. Lepitil contains the active phenobarbital and is indicated for the treatment of epilepsy in dogs. The product is administered orally with the dose dependent on the individual dog and the severity of the condition. The product is contraindicated in animals with known hypersensitivity, impaired hepatic function, renal or cardiovascular disorders as well as dogs weighing less than 6 kg.

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 slight reactions observed are indicated in the SPC[1].

The product is safe for the user, 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 benefit/risk analysis is in favour of granting a marketing authorisation.

[1] SPC – Summary of Product Characteristics

II. QUALITY ASPECTS

A. Composition

The product contains the active substance phenobarbital and the excipients lactose monohydrate, microcrystalline cellulose, magnesium stearate, maize starch, talc and grilled meat flavour.

The container/closure system consists of PVC/ aluminium foil blister strips of 10 tablets packaged in a cardboard carton containing 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 500 or 1000 tablets. Alternatively 500 or 1000 tablets are packaged in white HDPE containers with a polypropylene child resistant cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

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. The product is manufactured by blending the active substance with the excipients and then tableted by direct compression. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is phenobarbital, an established active substance described in the European Pharmacopoeia. A certificate of suitability has been provided for the active substance manufacturer. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

The excipients comply with the requirements of the relevant Ph. Eur. monographs. The grilled meat flavour is not the subject of a pharmacopoeial monograph and an in-house specification had been provided. Certificates of analysis were received for all excipients.

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

Scientific data have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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 tests include those for identification and assay of the active substance, identification of the grilled meat flavour, appearance, dissolution, friability, disintegration and microbial purity.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

G. Stability

The certificate of suitability provided for the active substance states a retest period of 36 months. 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 when stored under the approved conditions. Data were provided for two batches stored at 25°C/60%RH for 18 months and 40°C/75%RH for 6 months. A shelf life of 3 years has been established.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the finished product as packaged for sale is 3 years.
- Shelf life of divided tablets is 2 days.
- Divided tablets should be stored in the original pack. Any divided tablet portions remaining after 2 days should be discarded.
- Keep the blister in the outer carton.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics
Phenobarbital has a widespread depressant action on cerebral function. It produces sedative effects and has been demonstrated to have a protective action against epilepsy in humans and corresponding animal models.

Seizures are considered to occur due to uncontrolled, continuous firing at the synapses of brain neurones. Phenobarbital is thought to prevent seizures by acting directly on the $GABA_A$ receptors[2] on neurones, which increases the flow of chloride ions into the cell, hyperpolarising the neurone and temporarily preventing the transmission of further neuronal signals.

Phenobarbital is also thought to have a second mechanism of action. It decreases the interneuronal sodium ion concentrations, inhibiting calcium ion influx to the neurone and inhibits the re-uptake of norepinephrine, a neurotransmitter. These two mechanisms of action act to reduce neuronal excitability and increase the motor cortex's threshold for electrical stimulation, which decrease monosynaptic transmission in the brain and result in the anti-convulsive effect of phenobarbital.

Pharmacokinetics

Phenobarbital is rapidly absorbed in dogs following oral administration. Maximal plasma concentrations are reached within 3 hours with bioavailability between 86-96%. Nearly half of the plasma concentration is protein bound. Phenobarbital is also known to cross the placental barrier and may be found in saliva and milk.

Phenobarbital is mostly metabolised in the liver by hydroxylated oxidation. It is a potent inducer of drug oxidation by increasing P450 enzymes and glucoronidation. This can lead to interaction with other drugs and increase their elimination. Approximately one third of phenobarbital administered is excreted unchanged in the urine.

Elimination half-lives of phenobarbital vary considerably between individuals, ranging from 40-90 hours. Steady state serum concentrations are reached 1-2 weeks after initiation of treatment.

Toxicological Studies

The applicant has provided published references and has evaluated studies which show that the toxicity of phenobarbital is well established and its use in human and animal medicine has been reported in the literature for several decades.

- Single Dose Toxicity

Studies looking at single dose toxicity have been included. The LD_{50}[3] value reported in dogs is 150 mg/kg when phenobarbital is administered orally. When phenobarbital is injected subcutaneously the lowest lethal dose is reported as 150 mg/kg.

[2] $GABA_A$ receptors – Ion channel receptors that respond to gamma aminobutyric acid
[3] LD_{50} – Half of the lethal dose

- Repeated Dose Toxicity

Studies conducted in laboratory animals were included. Adverse effects demonstrated by these animals were mainly changes in liver weight and enzymes and thyroid changes.

- Reproductive Toxicity, including Teratogenicity:

A review of published information was provided and it shows phenobarbital causes reproductive toxicity. Phenobarbital is reported to be a teratogen and developmental neurotoxicant in humans and experimental animals.

- Mutagenicity

Several references were reviewed regarding mutagenicity. Many tests have been performed looking at the genetic effects of phenobarbital *in vitro*, with the majority of tests being negative. The positive results showed no consistent pattern of genotoxicity and combined with the absence of direct evidence of phenobarbital interaction with DNA as well as negative *in vivo* data it is stated that phenobarbital can be considered to be a non-genotoxic agent.

- Carcinogenicity (if necessary):

Studies investigating the carcinogenic effects of phenobarbital were referenced. Laboratory studies show phenobarbital consistently produces hepatocellular adenomas and carcinomas in mice and hepatocellular adenomas in rats following lifetime exposure. Phenobarbital induces cytochrome P450 enzymes *in vivo* and stimulates cell proliferation in normal hepatocytes. It is reported to be a tumour promoter for rat and mouse liver. Phenobarbital is considered to be carcinogenic in laboratory animals.

Observations in Humans

Phenobarbital has been used to treat human epilepsy for many years and is stated to be the most widely used anti-epileptic worldwide. References provided indicate the most common adverse effect in humans is sedation. It is reported that sedation becomes less marked during continued administration. Other effects of phenobarbital include irritability and hyperactivity in children, confusion in the elderly, mood changes and rarely a rash. Administration of high doses of phenobarbital can result in nystagmus and ataxia as well as barbiturate induced respiratory depression. Toxic effects include coma, severe respiratory and cardiovascular depression, as well as hypothermia and skin blisters. There are also reports of hepatitis and liver disturbances following phenobarbital treatment.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the main risks of exposure are via hand to mouth contact following handling of the tablet and the more serious risk is from accidental ingestion. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- 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.
- Phenobarbital is teratogenic and may be toxic to unborn and breastfeeding 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 and prolonged skin contact with the product.
- Keep this product in its original packaging to avoid accidental ingestion.
- 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.
- 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.
- Wash hands thoroughly after use.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product contains a well-known active, would be used to treat individual dogs, and as the use was for non-food animals the risk of environmental exposure is minimal. 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

Pharmacology

Pharmacodynamics

Phenobarbital has a widespread depressant action on cerebral function, producing sedative effects and a protective action against human epilepsy and epilepsy in corresponding animal models.

Phenobarbital acts directly on the $GABA_A$ receptor at the postsynaptic cleft. At clinical concentrations phenobarbital is thought to prevent seizures by acting directly on the $GABA_A$ receptors to inactivate the Cl^- channel, increasing the flow of chloride ions into the cell, hyperpolarising the postsynaptic neurone and temporarily preventing the transmission of nerve impulses.

Phenobarbital is also thought to have biochemical actions such as decreasing the interneuronal Na^+ concentrations, inhibiting Ca^{2+} influx to the neurone and inhibits the re-uptake of norepinephrine, a neurotransmitter. These mechanisms of action of phenobarbital act to reduce neuronal excitability and increase the motor cortex's threshold for electrical stimulation, which decrease monosynaptic transmission in the brain and result in the anti-convulsive effect of phenobarbital.

Pharmacokinetics

Phenobarbital is rapidly absorbed in dogs following oral administration. Maximal plasma concentrations are reached within 3 hours with bioavailability between 86-96%. Phenobarbital is relatively lipid insoluble which delays the rate of absorption into the CNS[4] compared to other barbiturates. Levels of phenobarbital achieved in the CNS are 43-52% of the levels achieved in the plasma. Nearly half of the plasma concentration is protein bound. Phenobarbital is also known to cross the placental barrier and may be found in saliva and milk.

Phenobarbital is mostly metabolised in the liver by hydroxylated oxidation. It is a potent inducer of drug oxidation by increasing P450 enzymes and glucoronidation. This can lead to interaction with and increase the elimination of other drugs. Approximately one third of phenobarbital administered is excreted unchanged in the urine.

Elimination half-lives of phenobarbital vary considerably between individuals, ranging from 40-90 hours. Steady state serum concentrations are reached 1-2 weeks after initiation of treatment. The elimination of phenobarbital is increased when the volume and pH of the urine is increased. The half-life is increased and elimination delayed in liver disease. Administration of phenobarbital to dogs with impaired hepatic and renal function should be done so with caution.

Tolerance in the Target Species of Animals

The applicant has conducted a controlled target animal tolerance study using multiples of the recommended dose in the target species. The dogs were administered orally half a Phenobarbital 60 mg tablet twice daily for 14 days. Clinical observations, including general health, behaviour and appetite, were made twice daily following administration of the product during days 0-14 and for a week before and after the study. Clinical examinations took place a week before the study, on day 0 and on day 14. These examinations were performed to check for changes to the dog's behaviour, temperature, musculo-skeletal, respiratory, genito-urinary, digestive, neurologic or cardiovascular system. No adverse effects were seen following doses up to half a tablet administered twice daily for 14 days, indicating phenobarbital is well tolerated in the target species at this level.

Bibliographical data have also been provided which give a comprehensive overview of the side effects commonly seen following phenobarbital administration. The side effects include polyphagia, polyuria and polydipsia as

[4] CNS – Central Nervous System

well as lethargy most commonly and these are normally transitory. When phenobarbital levels reach the higher limits of the therapeutic range sedation and ataxia can become significant concerns. The literature also reports raised liver enzyme levels and records rare cases of anaemia, thrombocytopaenia, neutropenia and osteomalacia following sustained high levels of phenobarbital. Phenobarbital overdose can be fatal and toxic effects include coma, respiratory and cardiovascular depression and shock leading to renal failure. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

Information and studies investigating the development of resistance of the anti-seizure effects in rats have been included. It has been reported that in human medicine 20-30% of patients with epilepsy are pharmacoresistant. This is attributed to the over-expression of P-glycoprotein, a multi-drug resistant protein, in the brain. In a study in rats a good anti-epileptic effect was observed initially following treatment with phenobarbital, however after continuous treatment a gradual reduction in the anti-epileptic effect was noted. This change corresponded to an increase in P-glycoprotein expression and a decreased concentration of phenobarbital in the brain. Whilst resistance to the anti-epileptic effect of phenobarbital is displayed by some individuals it is still the most widely used and an effective treatment for idiopathic epilepsy in dogs.

IV.B Clinical Studies

As this product is a generic hybrid, where bioequivalence cannot be demonstrated through bioavailability studies, the results of dissolution studies are supplied. No further studies were required.

The applicant has provided a comparative dissolution study between the test product and the reference product, Epiphen 60 mg Tablets. The dissolution profiles of the two products were compared at different pH conditions, neutral, acidic and very acidic. The dissolution study was performed under standard conditions and repeated 12 times at each pH. One tablet was used on each occasion. The solution was sampled at 5, 10, 15, 45 and 60 minutes. Analysis of each sample was done using a validated HPLC method in accordance with VICH Guidelines.

The results of the experiments show both the test and reference products achieved over 85% dissolution within 15 minutes in each of the three pH conditions. The study demonstrates the rapid solubility of the test product and that the dissolution profile of the test product is similar to the dissolution profile for the reference product.

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)