Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Epirepress 60 mg Tablets for Dogs

Date Created: 11th March 2016

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Epirepress 60 mg Tablets for Dogs
Applicant	Desitin Arzneimittel GmbH Weg beim Jäger 214 22335 Hamburg Germany
Active substance	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 Product Information Database of the Veterinary Medicines Directorate.

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Bibliographic application in accordance with Article 13(a) of Directive 2001/82/EC as amended.

I. SCIENTIFIC OVERVIEW

Epirepress 60 mg tablets for dogs are intended for the prevention of seizures due to generalised epilepsy. This application was submitted under Article 13 (a) of Directive 2001/82/EC as amended, for a product supported by bibliographic data showing 'well-established use'.

The product is intended for the prevention of seizures due to generalised epilepsy in dogs.

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, any 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 [2] 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.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 60 mg phenobarbital per tablet, and the excipients cellulose microcrystalline, maize starch, gelatin, lactose monohydrate, stearic acid and silica colloidal anhydrous.

The container/closure system consists of brown glass containers (glass Type III with a white, child-resistant polyethylene stopper in a carton, or a white polyethylene container with a white, child-resistant polypropylene screw cap in a carton. The product is produced in pack sizes of 30, 60 or 120 tablets. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the absence of preservative are justified.

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

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a wet granulation process, with the final blend being tableted and packed into the packaging material. Suitable validation of the manufacturing process takes place.

II.C. Control of Starting Materials

The active substance is phenobarbital, an established active substance described in the European Pharmacopoeia (Ph. Eur). 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, an acceptable Certificate of Suitability was also provided. All excipients are monographed in the Ph. Eur.

II.C.4. Substances of Biological Origin

A TSE declaration has been provided, stating that Epirepress 60 mg tablets comply with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicinal products. The only components of animal origin are lactose monohydrate, calf rennet and gelatin (from pigs). Suitable declarations were received affirming the quality of the cattle –derived substances used. Pigs are not a TSE-relevant species.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. 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. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specification. Control tests on the finished product include those for appearance, disintegration, crush resistance, uniformity of dose units, friability, loss on drying, phenobarbital identification and assay, dissolution, degradation products and microbiological quality.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Tests showed that phenobarbital is stable in suitable packaging for 6 years at 25°C/60% RH and for 6 months at 40°C/75% RH. A retest period of 5 years was agreed. For the finished product, comprehensive real-time and accelerated study data supported a shelf-life of the product presented unopened, contained in both pack types, for 3 years.

G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 3 months.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

This application was submitted under Article 13(a) of Directive 2001/82/EC as amended for 'well-established use'. The supporting data were publicly available bibliographic references, many of which were used to support the pharmacological and toxicological requirement of the human product, Phenaemal 0.1 Tablets/Phenaemaletten Tablets.

III.A Safety Documentation

Pharmacological Studies

Pharmacodynamics

Phenobarbital is an anticonvulsant barbiturate. The key mechanism of action is via the inhibition of GABA[3] neurotransmission, which provides a positive effect in the control of different types of epilepsy. Secondary pharmacodynamic actions include sedation, incoordination, reduction in memory and learning ability and effects on bilirubin and glucose metabolism.

Pharmacokinetics

Following oral administration to dogs, rapid absorption occurs, and maximum plasma concentration generally attained within 4-8 hours. Bioavailability is high, at approximately 86-96%. The active substance is rapidly distributed, with particularly high concentrations seen in the liver, kidneys and brain. Approximately a third of the drug is excreted via the kidneys, unchanged. Metabolites are also found.

Toxicological Studies

The applicant provided bibliographical data.

- Single Dose Toxicity

An LD_{50}[4] value presented for dogs given a single dose of phenobarbital was 150 mg/kg.

- Repeated Dose Toxicity

No NOAEL[5] data are available in published literature for this active substance. Studies in rats and mice revealed adverse effects at overdose included thyroid hyperfunction, liver weight changes and increase in CYP[6] levels.

- Reproductive Toxicity, including Teratogenicity:

Provided literature describes adverse effects of phenobarbital on offspring. The SPC carries suitable warnings.

[3] GABA – γ-aminobutyric acid.
[4] LD_{50} – Dose at which half a test population are terminated.
[5] NOAEL – No observed adverse effect limit.
[6] CYP – Cytochrome P450 enzyme family.

- Mutagenicity

No genotoxic mutation was noted in the Ames test. Limited numbers of chromosomal aberrations were noted in mouse studies.

- Carcinogenicity

It is known that hepatic tumours are seen in rodents when phenobarbital is administered. No evidence of this is seen in humans.

Observations in Humans

Bibliographical data were provided. The many sedative and neurological effects of phenobarbital are a particular risk for children and pregnant women. When the active substance is used in humans, tolerance to adverse effects is mitigated after a few days by acquired tolerance. Physical dependence may be acquired following prolonged use. The SPC carries suitable warnings.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Data were provided which highlight the effects of overdose of phenobarbital. Symptoms include progressive neurological depression and stupor which can be fatal, with the possibility of severe consequences more significant for people who have not been previously exposed to phenobarbital. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Both human and animal studies have shown that adverse effects from phenobarbital has been seen in neonatal and prenatal studies. Information was received on toxicity of the excipients, and appropriately assessed. Possible scenarios for ingestion of the active substance were assessed, and suitable risk management considered. The SPC carries suitable warnings:

- People with known hypersensitivity to barbiturates should avoid contact with this veterinary medicinal product.

- 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.

Environmental Safety

A Phase I environmental risk assessment conducted in accordance with VICH[7] guideline stated that the product would be used for individual animals in a non-food species. There was no requirement for further data. The disposal advice in the SPC and product literature includes a reference to the Misuse of Drugs Regulation 2001, as phenobarbital is a schedule 3 controlled drug.

IV CLINICAL DOCUMENTATION

The applicant referred to published literature in support of this application. These data satisfied the requirement for the legal basis of the application, and confirm the well-established use of phenobarbital.

IV.I. Pre-Clinical Studies

Pharmacology

The applicant has provided suitable bibliographical data, describing the pharmacodynamic and pharmacokinetic properties of phenobarbital. Possible, significant drug interactions have been described, and the SPC carries suitable warnings.

Tolerance in the Target Species

The applicant provided data describing the wide inter-subject variation that may be seen in dogs given phenobarbital. Significant data highlighted that daily oral treatment was tolerated to approximately three times the recommended minimum dose, including 11 mg/kg for 90 days, 17 mg/kg for up to 32 months and up to 13 mg/kg for up to 25 months. The lowest recommended dose is 5 mg/kg given in two equal portion, with dose adjustment performed on the basis of clinical efficacy. The SPC carries the warning that the required dose will differ to some extent between individuals and with the nature and severity of the disorder.

The product literature accurately reflects the type and incidence of adverse effects which might be expected, and describes where use of the product is contraindicated.

[7] VICH - Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

IV.II. Clinical Documentation

The applicant provided bibliographical data. Six references reported clinical studies discussing the control of canine seizures caused by generalised epilepsy. Four of the studies were controlled studies where overall treatment efficacy, (percentage of dogs in which complete control of the condition was achieved plus those where a 75% reduction in seizure occurrence was seen), for phenobarbital ranged from 71% to 80%. In a study where animals were treated with phenobarbital or primidone, 35% to 48% of animals were fully responsive to phenobarbital, and 39% to 52% were fully responsive to primidone. IN another study, phenobarbital treatment attained complete control of seizures in 85% of cases, as opposed to 52% for potassium bromide (KBr) treatment.

The minimum dose of phenobarbital required to totally control or adequately reduce seizures ranged from 2 mg/kg to 10 mg/kg. The maximum daily dose was between 10 mg/kg and 17 mg/kg. Doses were generally provided in two equal portions, 12 hours apart. The SPC provides appropriate information on starting dose (2.5 mg/kg administered twice daily), and recommends adjustments to dose are made on the basis of clinical efficacy, blood analysis and any associated adverse reactions.

In studies, the effective dose ranged from 11 µg/ml to 52 µg/ml. The phenobarbital serum concentration considered to be therapeutically active, and that which is described in the SPC, is between 20-40 µg/ml. It was noted that there is a large difference to response between animals provided with phenobarbital, even when the serum concentration of the active substance was the same. Steady state serum concentrations are not generally reached until 1 -2 weeks after the start of treatment, and doses should not be increased during this time. Data were satisfactory for assuring the efficacy of the product when used as directed.

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 of the product(s) is favourable

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.

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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.

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