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

Epilease 250 mg Capsules for Dogs

Date Created: July 2016

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Epilease 250 mg Capsules
Applicant	VetPlus Ltd Docklands Dock Road Lytham Lancashire FY8 5AQ
Active substance	Potassium bromide
ATC Vetcode	QN05CM11
Target species	Dogs
Indication for use	This product is indicated for use as an anti-epileptic therapy adjunct to phenobarbital in refractory cases of 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	Full application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.

I. SCIENTIFIC OVERVIEW

This was a full application under Article 12 (3), according to Directive 2001/82/EC, as amended. Assessment followed EMA guidelines on data requirements related to MUMS[1] applications.

Epilease 250 mg Capsules for dogs is indicated for use as an anti-epileptic therapy adjunct to phenobarbital in refractory cases of epilepsy in dogs. The dose is initially 15 mg/kg bodyweight twice daily, (equivalent to a total daily dose of 30 mg/kg). It may take several weeks or months to attain steady-state serum concentrations. Use of the product in dogs of less than 16.67 kg should be assessed in accordance with the Summary of Product Characteristics (SPC), section 4.5.

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. 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] MUMS – Minor Use Minor Species.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 250 mg potassium bromide per capsule and excipients as follows: brown rice flour, magnesium stearate, capsule body, gelatine, titanium dioxide, FD&C Red 3 (E127) and Quinoline Yellow (E104). The capsule cap contains gelatine, titanium dioxide, and FD&C Blue 2 (E132).

The container/closure system consists of triplex PVC with foil. Blister packs contain 30 capsules on each blister strip. There are two blister strips to a carton, giving a pack size of 60 capsules. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and 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 simple sieving and mixing process, followed by filling into drums and encapsulated. The capsules are then placed in blisters.

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

II.C. Control of Starting Materials

The active substance is potassium bromide, 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. The active substance specification is supported by appropriate Certificates of Suitability. Excipients are suitably documented.

II.C.4. Substances of Biological Origin

Certificates of Suitability have been provided for the gelatine used within the capsule. This was considered acceptable.

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 site have been provided demonstrating compliance with the specification. Control tests on the finished product include those for appearance, identity of active substance, uniformity of mass, microbial purity and disintegration,

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 and finished product when stored under the approved conditions.

G. Other Information

- Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
- Do not store above 25°C.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Relevant bibliographical data have been provided.

Pharmacodynamics

It is thought that bromide acts in a similar fashion to GABA (γ-aminobutyric acid), whereby specific neuronal excitability is controlled, and neurones are then stabilised via hyperpolarisation, reducing the effect of seizures.

Pharmacokinetics

Bibliographical data with regard to the pharmacokinetic properties of bromide in humans, horses and dogs have been provided. Potassium bromide dissociates in water into its constituent ions, which are passively absorbed. In dogs,

bioavailability is approximately 46%. In animals administered 30 mg/kg 2 times a day, serum bromide increases with time, the steady-state concentration being attained at approximately 50 days. Distribution is wide following absorption, and is stated as being 0.3 – 0.4 l/kg in the dog. Bromide is a simple ionic salt and is therefore excreted unchanged. The elimination half-life of bromide given to dogs for 115 days was shown to be approximately 15 days, with total body clearance shown as being 16.4 ml/day/kg. Additional studies have demonstrated a half-life of 46 and 37 days for dogs provided bromide for oral and intravenous administration respectively. Excretion is performed almost entirely in the kidneys.

Toxicological Studies

The applicant provided suitable bibliographical data.

- Single Dose Toxicity

Bibliographical data were provided, showing relevant LD_{50} data with relevance to sodium bromide and potassium bromide.

Species	**Oral LD_{50} (mg/kg bw/day)**		
	Sodium bromide	**Bromide equivalent**	**Potassium bromide equivalent**
Rat	3500	2718	4048
Mouse	5020	3899	5806
Mouse	7000	5436	8096

- Repeated Dose Toxicity

Three bibliographical studies were provided which showed that in rats the toxicity of bromide was seen to be approximately 10 x higher in rats given a low chloride dose, as compared to animals provided a normal diet.

In two 4-week studies where animals were provided with up to 19,200 mg/kg bromide, A NOEL[3] of 300 mg/kg was noted for animals on a normal diet, but a NOEL of 1200 mg/kg was noted where animals were on a low chloride diet (3 g/kg as opposed to 11 g/kg). A further 90 day study where rats were maintained on 0.4 – 0.7 g/kg chloride in the diet demonstrated a NOEL of 125 mg/kg.

- Reproductive Toxicity, including Teratogenicity

A 3-generation rat study was cited. At high doses 19,200 mg/kg or 746 mg/kg/day the fertility of both sexes was decreased. It was concluded that the NOEL for effects of reproduction was 4800 mg/kg/day. Significantly higher than the dose proposed for the product. It was therefore concluded that it was unlikely that there would be adverse effects with regard to fertility in dogs.

[3] NOEL – No observed effect level.

- Mutagenicity

In the studies previously described, there was no evidence of teratogenicity. In addition, no reports of teratogenicity have been described in humans using bromide for the control of epilepsy.

- Carcinogenicity

No evidence was presented implying that bromide is carcinogenic.

Observations in Humans

The recommended dose of bromide in humans, for use as a sedative anticonvulsant, is up to 6 g/day. Bromide is no longer used in humans in the UK. Signs of toxicity to bromide include vomiting and nausea, abdominal pain, and paralysis and coma. Doses above 40 mmol/l (320mg/l) may prove fatal. Psychiatric symptoms and neurological complications may be observed. In one study cited, 20 healthy volunteers, 10 males and 10 females, were given sodium bromide orally at 1 mg/kg/day for 8 weeks. As plasma concentration increased, there were no effects observed on a variety of relevant parameters. A second study observed groups of 7 males and females dosed for 7 weeks at 0, 4 or 9 mg/kg/day. Serum concentrations of triidothyronine and thyroxine at the conclusion of the study were greatly increased in females, but were within normal range. Suitable data were provided on eye irritation and skin sensitivity. The SPC provides suitable warnings in relation to administration of the product to dogs by humans.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- Do not break capsules.
- Do not use this product if you have known sensitivity to bromide.
- Discontinue handling this product if you develop any signs of skin irritation, including itchiness, rash, peeling or flaking of skin or redness. Seek medical attention if irritation persists, showing the physician the carton or package leaflet.
- If this product is ingested, seek medical attention immediately and show the physician the carton or package leaflet.
- Wash hands thoroughly immediately after handling and/or administering the product.
- Advice to doctor: Bromide intoxication can be treated by administration of sodium chloride or a suitable chloruretic agent.

Environmental Safety

An acceptable Phase I Environmental Risk Assessment was provided. The product is to be used in individual dogs only, and is not expected to pose a risk to the environment when used as recommended.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

The applicant provided bibliographical references in relation to pharmacodynamic and pharmacokinetic data.

Pharmacodynamics

A halide anticonvulsant, bromide replaces chloride in all body fluids, competing with chloride transport across nerve cell membranes, and inhibiting sodium transport. This causes membrane hyperpolarisation. Hyperpolarisation raises the seizure threshold, preventing the spread of epileptic discharges. Bromide affects active transport across ganglial cell membranes, and also affects passive movements of ions by competition with chloride for anion channels in post-synaptic membranes activated by inhibitory neurotransmitters. This potentiates the effect of GABA, which results in the synergistic activity of bromide with other drugs that have GABA-ergic activity, for example, phenobarbital.

Pharmacokinetics

The pharmacokinetics of potassium bromide has been studied in dogs. The half-life is approximately 24 days, but varies with dietary chloride content. Due to this long half-life, it may take several weeks and/or months to achieve steady state serum concentrations. Potassium bromide is well absorbed orally, with peak absorption in about 1.5 hours. Following ingestion, the potassium bromide salt dissociates, and is rapidly absorbed by the gastrointestinal tract.

Following absorption, the bromide ion rapidly distributes, in a similar manner to that of chloride, throughout the extra-cellular space and into cells. Chloride is distributed passively across most cell membranes according to the trans-membrane potential, and it is likely that bromide is distributed in the same manner. As the bromide level increases in the body, the concentration of chloride is decreased in direct proportion to the increase in bromide.

Bromide is not metabolised by the body, it enters and leaves the body only as the monovalent anion. It is eliminated from the body by the kidneys, and is not cleared by the liver. It may therefore be used in dogs with compromised hepatic function.

Tolerance in the Target Species

A target animal safety study and bibliographical data were provided. Target animal safety was sufficiently demonstrated following submission of a comparative pharmacokinetic study and two dissolution studies (see section IV.II for further detail) which bridged the bibliographic data to the candidate product formulation.

IV.II. Clinical Documentation

The applicant submitted suitable bibliographic references in relation to dose justification for the proposed product and reviews of cases of clinical epilepsy in dogs attending veterinary practices identified by the applicant. In order to bridge the bibliographic data to the candidate product formulation, a comparative pharmacokinetic study and two dissolution studies were provided.

The pharmacokinetic study compared the pure active substance, potassium bromide solution (4% w/w), with Epilease 100 mg Capsules. In this parallel design, multi-dose, two-stage study, 16 dogs, 8 males and 8 females, with bodyweight 8.40 kg – 9.96 kg and 7.53 – 9.09 kg respectively were divided into 2 groups and given either Epilease 100 mg Capsules or 4% w/w potassium bromide. The dogs were 7-8 months old, were established as being appropriately healthy prior to treatment and acclimatised at the test premises for 2 weeks prior to the start of treatment. The animals were fed immediately after dosing, and males and females were randomised separately, stratified according to recent body weight, to give 4 of each sex in each group. Concurrent treatment with phenobarbital, (Phenoleptil), was also given.

The dose regimen was approximately 30 mg/kg potassium bromide/kg divided into two daily doses, given directly before feeding for 90 consecutive days. In Group 1, each dog received either 1 or 2 capsules of 100 mg Epilease Capsules every 12 hours. In Group 2, each dog received 2.5 or 5 ml potassium bromide solution every 12 hours, based on recently determined bodyweight. Phenoleptil was given to both groups at 2.5 mg/kg/12 hours for 105 days, starting 14 days before treatment with potassium bromide. Total dietary chloride consumption was controlled to 120 mg/kg/day for each animal.

Blood samples were taken for analysis at suitable time points. Appropriate statistical analysis was performed primarily to determine sufficient similarity between pharmacokinetic characteristics, rather than demonstratebioequivalence. The pharmacokinetic parameters were sufficiently similar between the groups to bridge the candidate product formulation to the bibliographic data provided.

In addition, two dissolution studies were performed which demonstrated the similarity of dissolution between Epilease 100 mg and Epilease 250 mg Capsules for Dogs. With the combined data submitted, product efficacy was confirmed and the application was approvable.

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.

(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)