IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Libromide 325 mg tablets for dogs

PRODUCT SUMMARY

EU Procedure Number	IE/V/0507/001 (formerly UK/V/0400/001)
Name, Strength, Pharmaceutical Form	Libromide 325 mg tablets for dogs
Active Substances(s)	Potassium bromide
Applicant	Dechra Regulatory B.V., Handelsweg 25, 5531 AE Bladel, Netherlands
Legal Basis of Application	Full application (Article 12(3) of Directive No 2001/82/EC)
Target Species	Dogs
Indication For Use	An antiepileptic agent for use as an adjunct to phenobarbital in the control of refractory cases of epilepsy in dogs.
ATC Code	QN05CM11
Date of completion of the original mutual recognition procedure	28 September 2011
Date product first authorised in the Reference Member State (MRP only)	04 February 2010 (UK) 18 November 2011 (IE)
Concerned Member States for original procedure	Belgium Czech Republic Denmark Finland Germany Hungary Ireland (now RMS) Italy The Netherlands Norway Poland Spain Additional CMS added for Repeat Use procedure: Austria, France, Sweden. UK added via RMS change

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

Libromide 325 mg tablets for dogs is authorised for use in dogs. The product is indicated for use as an antiepileptic agent for use as an adjunct to phenobarbital in the control of refractory cases of epilepsy in dogs. Each tablet contains potassium bromide 325 mg as an active substance.

The application was submitted in accordance with Article 12.3 of Directive 2001/82/EC, as amended by 2004/28/EC (a 'full' application). Libromide 325 mg tablets for dogs was first authorised in the UK on 4th February 2010 as a National Marketing Authorisation, with a request to be considered as a Limited Markets (minor use) application because refractory cases of epilepsy in dogs, where treatment is required in addition to first line treatment with phenobarbitone, are uncommon to rare and recurrent seizures are distressing for both dog and owner, reduce the quality of life and can be life-threatening. This was considered acceptable.

The product is intended for use as an adjunct to phenobarbital in the control of refractory cases of epilepsy in dogs. The product is intended to be administered at an initial dose of 15 mg/kg bodyweight twice daily with food, equivalent to a total daily dose of 30 mg/kg. For at least the first three months following commencement of therapy, the serum bromide concentrations should be measured every 4 weeks. The expected serum bromide concentration when used in conjunction with phenobarbital is 800 to 2000 µg/ml. Adjustments to the dose should be made with regard to the frequency of seizures, the half-life of bromide and the serum bromide concentration. For dogs with a bodyweight of 11 kg or less the dose regimen may need to be adjusted by the prescribing veterinarian, with due consideration given to the pharmacokinetics of the active substance, therapeutic serum bromide levels, clinical effect and a benefit/risk assessment.

The product is presented in white, polypropylene container with polypropylene, tamper-evident, push-fit closure containg either 100 or 500 tablets.

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. 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.

II. QUALITY ASPECTS

A. Composition

The product contains the active substance potassium bromide and the excipients lactose monohydrate, microcrystalline cellulose, magnesium stearate, stearic acid and sodium saccharin.

The product is an established pharmaceutical form and its development has been 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 applicant has provided details of the stages of and method of manufacture. In-process controls have also been described. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance potassium bromide complies with the requirements of the monograph of the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice. The active substance specifications are considered adequate to control the quality of the material.

All excipients are described in the European Pharmacopoeia. The applicant appropriately applies the current monograph of the European Pharmacopoeia as the specification for each ingredient of the finished product. A specimen supplier's certificate of analysis showing the compliance of one batch of each material has been supplied.

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

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

There are no intermediate products.

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.
Satisfactory validation data for the analytical methods have been provided.

G. Stability

The applicant has demonstrated that the active substance is unreactive in its dry state. A retest interval of 24 months is accepted for material stored in unopened containers in a cool dry place.
No stability data on the in-use stability have been provided. This is considered acceptable as halved tablets are likely to be quickly used.
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.
A shelf life of 3 years is justified with no special precautions for storage.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Special precautions for storage:

- This product does not require any special temperature storage conditions.
- Keep the tablet container tightly closed in order to protect from moisture.

Shelf-life:

- Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
- Use any halved tablet within 12 hours.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided a number of published references including CVMP[1] MRL summary reports to support the pharmacology of potassium bromide. The CVMP MRL summary reports for potassium bromide confirm that the potassium ions possess no toxicity after oral administration and any toxicity of the salt is associated with the anion. The toxicity of the bromide ion has been considered in relation to sodium bromide. This report also states that the potassium is a normal component of the diet and is particularly abundant in fruit and vegetables. The recommended daily intake varies from 350 to 1275 mg in children to 1875 and 5625 mg in adults. In the UK, the reference nutrient intake (RNI) is 3.5 g/day for adults.

Pharmacodynamics

The applicant has submitted seven published references, which support the activity of potassium bromide alone, or as an adjunct with phenobarbital in dogs with epilepsy. Potassium bromide is regarded as an anticonvulsant medication in dogs. Potassium bromide can be used, either as first-line treatment, or in addition to phenobarbital when the seizures are not adequately controlled with phenobarbital alone. Potassium bromide competes with chloride ions for access to brain tissues. As bromide levels in the brain rise and chloride levels drop, electrical activity in the central nervous system is inhibited, reducing the likelihood of seizure initiation.

Pharmacokinetics

The applicant provided data on the bromide serum levels attained when the product was used in conjunction with phenobarbitone during a GLP[2] tolerance study. In addition, the applicant has submitted a literature review of relevant studies in humans, dogs and rodents in support of this application. The literature references demonstrate that following oral ingestion by humans the potassium salt dissociates and the bromide is subsequently rapidly absorbed from the intestinal tract in a manner similar to chloride. In particular, the absorption occurs in the small intestine and since no bromide is excreted in the faeces, the entire orally administered dose is absorbed into the bloodstream. In the dog, the oral and intravenous (IV) routes of administration of bromide have been studied. Absorption has been shown to be rapid, reaching peak serum concentration in 30 to 45 minutes after oral administration. Estimated oral bioavailability based on the average mean AUC values for both routes of administration was 46%. Following oral and IV administration, the bromide ion rapidly distributes (within 2 hours) throughout the extra-cellular fluid.

Bromide very rapidly diffuses from the extracellular fluid into tissues and organs until equilibrium with the concentrations in the extra-cellular fluid is reached. Bromide is not metabolised by the body; it enters and leaves the body as a monovalent anion.

Bromide is mostly excreted in the urine but can also be excreted in small amounts in skin, nasal and conjunctival secretions, and in saliva. No bromide is excreted in the faeces. The elimination of bromide by normal human subjects is slow, with a half-life of around 12 days when chloride intake by diet is not controlled. The elimination of bromide in dogs is slower than that seen in humans, with one study demonstrating a half-life of around 33 and 39 days for IV and oral routes, respectively. In the literature, other elimination half-lives range between 15 and 68 days depending on the daily dose administered, the duration of treatment, the time of sampling bloods and the chloride content in the diet. High levels of chloride intakes have been shown to enhance the elimination of bromide in dogs, rodents and humans.

The applicant has provided further data on the pharmacokinetics of potassium which states that the potassium is the major cation inside animal cells and is important in maintaining fluid and electrolyte balance in the body. Potassium salts are generally readily absorbed from the gastrointestinal tract. Potassium is essential in maintaining cellular tonicity, nerve impulse transmission, smooth skeletal and cardiac muscle contraction and maintenance of normal renal function. Potassium is excreted mainly by the kidneys (80-90%); it is secreted in the distal tubules in exchange for sodium or hydrogen ions. The majority of the remainder is excreted in the faeces.

Toxicological Studies

Single dose toxicity:

In the interest of animal welfare and due to the abundance of acute toxicity information available in the public domain for the active ingredient, the applicant proposed not to conduct any single dose toxicity studies. The applicant has referred to the CVMP MRL[3] summary report on sodium bromide. This summary report describes LD50[4] tests in rats and mice and presented the following results:

Species	**Route of Administration**	**LD_{50} (mg/kg bw)**
rat	oral	3500
mouse	subcutaneous	5020
mouse	oral	7000

The applicant also refers to the published data which presented the following results:

Species	**Route of Administration**	**LD_{50} (mg/kg bw)**
mouse	oral	3120
rat	oral	3070
mouse	intraperitoneal	1030
guinea pig	intraperitoneal	980

Acute studies in rodents have indicated a very low toxicity for bromide. The applicant has stated that the LD50 values published for potassium bromide in other species and for the other routes of administration were derived from Material Safety Data Sheets. This is considered acceptable and no further information is required.

Repeated dose toxicity:

Two studies were described in the CVMP MRL summary report on sodium bromide. These studies were conducted on rats and demonstrated that at higher doses there were increases in the weights of the thyroid, adrenals and prostate glands, which were matched by evidence of increased secretory activity of these organs. High doses also produced more general signs of toxicity such as poor grooming, motor incoordination and growth retardation. There was also an increased neutrophil count. At lower doses, no adverse effects were seen. The applicant also conducted a repeat dose study as part of the target animal safety study.

Other Studies

Reproductive toxicity (inc. teratogenicity)

The applicant has not conducted any specific reproductive toxicity studies using Libromide 325 mg tablets for dogs. The applicant referred to the CVMP MRL summary report on sodium bromide which describes a three generation rat reproduction study, and states that at the highest doses tested of 4800 mg/kg (186 mg Br /kg bw/day) and 19200 mg/kg (746 mg Br /kg bw/day) of sodium bromide, the fertility of both male and females was decreased. The applicant compared these levels to the potential maximum dose of Libromide 325 mg tablets for dogs to be administered to a 57 kg dog (33 mg Br/kg bw/day) and reported a 5 fold difference. Due to this difference, the applicant states that Libromide 325 mg tablets for dogs are unlikely to have reproductive toxicity effects. The study confirmed that bromide is not teratogenic. Bromide was shown to be capable of crossing the placenta to the foetus. There was no evidence of mortality to embryos or foetuses and examination of the pups at birth showed no gross malformations.

Mutagenicity

No specific mutagenicity studies were conducted using Libromide 325 mg tablets for dogs. The applicant referred to the CVMP MRL summary report for sodium bromide which describes limited AMES tests[5] on sodium bromide and on ammonium bromide in Salmonella typhimurium strains TA98 and TA100, with and without metabolic activation. All the results were negative and therefore sodium bromide is not regarded as mutagenic. The data submitted were considered acceptable.

Carcinogenicity

No specific laboratory studies were submitted to determine the carcinogenicity of Libromide 325 mg tablets for dogs. As outlined in the CVMP MRL summary report for sodium bromide, there were no carcinogenicity studies. As a well characterised

ionic element and given the negative mutagenicity results, no further data were required.

Observations in Humans

Both potassium and sodium bromide have previously been used extensively in human medicine as sedatives, anticonvulsants and to treat epilepsy at doses of up to 6 g/person/day (100 mg/kg/day). Sodium and potassium bromide are no longer authorised for use in humans in the UK. The CVMP MRL sodium bromide summary report describes a series of studies conducted in human volunteers. The administration of 9 mg Br/kg bw/day resulted in increased serum levels of the total and free thyroid hormone T4. No effect was seen at 7 mg Br/kg bw/day. The results indicate a NOEL[6] of 4 mg Br/kg bw/day and an ADI[7] of 0.4 mg/kg bw (0-24 mg/person for humans) has been determined.

User Safety

The applicant has provided a satisfactory user risk assessment, identifying the users of the product and the potential routes of exposure for the operator. The risks have been identified and appropriate warnings are included in the SPC and product literature. These are:

•Do not handle this product if you are pregnant, think you are pregnant or if you are breast feeding.
•Do not use this product if you have a known sensitivity to bromide.
•Wash hands thoroughly immediately after breaking or handling any tablets.
•Discontinue handling this product if you develop any signs of skin irritation, including itchiness, rash, peeling or flaking of skin or redness. In case of irritation of the skin or eyes, or in case of accidental self-administration, seek medical advice immediately and show the package leaflet or the label to the physician.
•To the physician: Bromide intoxication can be treated by administration of sodium chloride or a suitable chloruretic agent.

Ecotoxicity

The products are only intended for administration to dogs. A Phase I environmental risk assessment was satisfactorily carried out in accordance with VICH and CVMP guidelines. Data provided have demonstrated that exposure of these products to the environment will not be extensive and the assessment can end at Phase 1.

III.B Residues documentation

The product is for a non-food producing species; therefore residues documentation is not required.

[1] Committee for Medicinal Products for Veterinary Use
[2] Good Laboratory Practice
[3] Maximum Residues Limit

[4] LD50 is the amount given at once, which causes the death of 50% (one half) of a group of test animals
[5] The AMES test is a biological assay to assess the mutagenic potential of chemical compounds.
[6] No Observable Effect Levels
[7] Acceptable Daily Intake

IV. CLINICAL ASSESSMENT

Pharmacology

The applicant has provided published references to support the pharmacology of potassium bromide. This is discussed under Part III.

Tolerance in the Target Species of Animals

The applicant has provided both published references and a GLP[1] Target Animal Study. The adverse effects of bromide reported in dogs include neurological, gastro-intestinal and skin effects. Commonly polydypsia, polyuria, polyphagia and sedation are reported following the start of therapy. Neurological effects include incoordination, ataxia and possibly behavioural changes. In cases and studies where phenobarbital is administered concurrently, it becomes difficult to determine whether the adverse effects exhibited are a direct result of the bromide or due to potentiation of the effects of the phenobarbital. If bromide doses continue to be increased stupor, coma and eventually death will ensue, however cessation of therapy in initial phases will lead to reversal of the clinical signs associated with toxicosis. Chloride loading may increase the speed of response. Other factors that affect the pharmacokinetics of bromide will also alter individual sensitivity, such as hydration and renal insufficiency. Observations have been made that indicate epileptic dogs on combined therapy may have reduced serum total and free T4 concentrations, although this may be related to the phenobarbital component of the therapy.

The applicant conducted a target animal safety study to assess the safety of Libromide 325 mg tablets for dogs administered in conjunction with phenobarbital tablets in beagle dogs. This was a randomised, blinded single centre GLP study. A suitable number of dogs were divided into different treatment groups. All treatment groups received phenobarbital tablets administered twice daily immediately after food, in accordance with the instructions on the authorised SPC, in order to achieve serum levels of phenobarbital within the recommended therapeutic range. After 21 days of phenobarbital treatment, additional therapy with Libromide 325 mg tablets for dogs was started. The treatment groups received daily doses of 30, 60 or 90 mg/kg. The daily dose was divided and administered twice daily immediately after

food. The dogs were treated for a suitable number of days, at which point a suitable number of dogs from the phenobarbital group and from the 60 mg/kg libromide group were randomly selected for a further 90 days follow-up. Basic health parameters, clinical examinations, haematological, clinical chemistry and serum levels of phenobarbital and KBr were monitored at intervals throughout the study. The study concluded that no treatment-related adverse events were observed. Two dogs had brief adverse events. This was diagnosed as a non-treatment related infectious gastro-enteritis, with a consequent leucocytosis. Increases in urea, serum alkaline phosphatase, globulin, serum total protein and a decrease in albumin were observed in all treatment groups and were potentially related to the administration of phenobarbital.

Resistance

Not applicable.

IV.B Clinical Studies

Laboratory Trials

The applicant has provided literature references and some qualitative field data to illustrate the field use of an identical formulation of the product as an adjunct therapy with phenobarbital in cases of canine epilepsy that are non-responsive to phenobarbital alone. The field data was collected from a suitable number of epileptic dogs in the United Kingdom. The product was used in accordance with the Veterinary Medicines Regulations Schedule 4 cascade.

The literature references provide evidence from defined retrospective analysis of field cases. They indicate that potassium bromide has a role to play in the treatment of refractory canine epilepsy cases. Although there is no agreed specific therapeutic serum bromide concentration level for efficacy versus safety and the sensitivity of an individual is variable, the target serum concentration level is consistent with the literature. Regular monitoring is advisable and the timings suggested are in accordance with the pharmacokinetic information. A clinical report of retrospective analysis of refractory canine epilepsy cases suggested that 78% of the dog owners were satisfied with bromide therapy for their pet, with regard to improved quality of life or decrease in seizure occurrence or severity.

An abstract in which the treatment of a suitable number of dogs with refractory seizures on high doses of primidone and/or phenobarbital that were then given potassium bromide at 17 to 58 mg/kg daily for 7 to 61 months is described. Seizure data from a suitable number of dogs were analysed: four became seizure free, seven had a reduction in seizure frequency of more than 50%, two had a reduction in seizure frequency of more than 50% but the number of seizure days reduced by less

than 50%. For the remaining dogs the therapy was unsuccessful. Serum concentrations differed even with the same dose among individual dogs. The therapeutic range of serum bromide concentration was 0.7 to 2.0 mg/ml. The authors recommend an initial daily dose for add-on therapy with potassium bromide of 30 to 40 mg/kg. During treatment the dose should be determined for each individual dog.

The applicant also described a study that aimed to compare the efficacy and side effects of potassium bromide and phenobarbital when used as a first line anti-epileptic drug in dogs. It is stated that the optimal therapeutic potassium bromide concentration to aim for initially is 15-20 mmol/l and that some dogs can have a higher potassium bromide concentration (up to 30 mmol/l) without significant side effects. The field use of Libromide 325 mg tablets for dogs in combination with phenobarbital indicated that when the product was administered in combination with phenobarbital the number of seizures decreased in the majority of dogs, with nearly half having 100% success in improvement i.e., the number of seizures was reduced to zero after treatment.

The published literature for the pharmacokinetic study in dogs indicated that to maintain bromide concentrations in the recommended therapeutic range of 1000 to 2000 mg/l, an oral dose of 21 mg/kg/day of sodium bromide would be required. If bromide is absorbed similarly from other bromide salts this is equivalent to 32 mg/kg/day of potassium bromide. A clinical pharmacology review in dogs indicated that the recommended starting dose is 10 mg/kg bodyweight every 12 hours given in food. The therapeutic range for bromide in serum was considered to be 10 to 20 mmol/l. Bromide concentrations should be monitored at 30 days, 120 days and then every 6 months after initiating therapy. Therapy must be individually tailored. A clinical report that cites other published papers states that the toxicity potential of bromide may be reduced by decreasing the dose or frequency of administration of bromide, when used in combination with other anti-convulsant drugs.
[1] Good Laboratory Practice

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.