Date of Approval: January 14, 2021

FREEDOM OF INFORMATION SUMMARY

APPLICATION FOR CONDITIONAL APPROVAL

Application Number 141-544

KBroVet®-CA1

potassium bromide chewable tablets

Dogs

KBroVet®-CA1 (potassium bromide chewable tablets) are indicated for the control of seizures associated with idiopathic epilepsy in dogs

Sponsored by:

Pegasus Laboratories, Inc.

Executive Summary

KBroVet®-CA1 (potassium bromide chewable tablets) is conditionally approved for the control of seizures associated with idiopathic epilepsy in dogs. Potassium bromide (KBr) is a halide salt, and when the salt passes through neuronal channels, it hyperpolarizes neuronal membranes and stabilizes the neurons. This reduces the likelihood of a seizure.

FDA determined that KBr was eligible for conditional approval under section 571(a)(1)(A)(ii) of the Federal Food, Drug, and Cosmetic Act because the drug controls a serious or life-threatening disease in dogs, addresses an unmet animal health need, and demonstrating effectiveness would require complex or particularly difficult studies. An animal drug that meets these criteria is eligible for conditional approval. A conditionally approved animal drug has been shown to be safe and have a reasonable expectation of effectiveness. During the conditional approval period, the sponsor can legally market the drug for the labeled use while collecting the remaining effectiveness data. The conditional approval is valid for one year. The sponsor can ask FDA to renew the conditional approval annually for up to four more years, for a total of five years of conditional approval. To receive a renewal from FDA, the sponsor must show active progress toward proving substantial evidence of effectiveness for full approval.

Proprietary Name	Established Name	Application Type and Number	Sponsor
KBroVet®-CA1	Potassium bromide chewable tablets	Conditional Approval Application Number 141-544	Pegasus Laboratories, Inc.

Safety and Reasonable Expectation of Effectiveness

The sponsor retrospectively evaluated the medical records of client-owned dogs that were previously treated with KBr to control their idiopathic epilepsy. To be included in the study, the dogs must have (1) received the same total daily dose of KBr for at least 60 days (this was considered to be steady state dosing conditions); and (2) received only KBr to control their seizures. Fifty-one eligible cases were identified, with 27 cases included in the evaluation of both safety and effectiveness and 24 cases included only in the safety evaluation.

Approximately 61% of the 51 eligible cases were male. The mean age of onset of epilepsy was 2.1 years and the mean age of starting KBr therapy was 2.4 years. Dogs had varying weights, and mixed-breed dogs were most common followed by Golden Retriever and Labrador Retriever, each comprising approximately 10% of the 51 cases.

For the 27 cases included in both the safety and effectiveness evaluations, the mean maintenance dose of KBr was 37 mg/kg/day. The dogs had been on this oral maintenance dose for a mean duration of 286 days. Effectiveness was evaluated by comparing change in seizure counts, seizure event days per month, and seizure severity scores in the 30-day period before starting KBr therapy to a 30-day period of steady state KBr dosing. Based on the effectiveness parameters, 67% (18/27 dogs) were treatment successes and 33% (9/27) were treatment failures.

For the 51 cases included in the safety evaluation, the mean maintenance dose was 40.2 mg/kg/day, and the dogs had been on this oral maintenance dose for a mean duration of 201 days. The most common adverse reactions seen in the initial dosing period (the 60 days after starting KBr therapy) were increased appetite, weight gain, vomiting or regurgitation, and sedation. The most common adverse reactions seen in the dosing phase (the 30-day period of steady state KBr dosing) were weight gain, weakness, ataxia, increased water consumption (polydipsia), increased appetite, and sedation.

The results of this retrospective study demonstrated that KBr has a reasonable expectation of effectiveness for controlling seizures in dogs with idiopathic epilepsy, at the recommended oral dose range of 25 to 68 mg/kg/day. The results also demonstrated that KBr has an adequate safety profile in dogs with idiopathic epilepsy.

To further support the drug's safety, the sponsor used the information available in a Public Master File that contains data describing the safety of KBr in dogs. FDA reviewed more than 50 years of published literature on the use of KBr in dogs, evaluating a total of 111 references. The agency published the results of this review in the *Journal of the American Veterinary Medicine Association* (Baird-Heinz HE, Van Schoick AL, Pelsor FR, et al. A systematic review of the safety of potassium bromide in dogs. *J Am Vet Med Assoc* 2012;240:705-715).

Based on the reviewed literature, the most common adverse reactions in dogs on KBr therapy were seen in the following body systems: neurologic, including behavioral changes; gastrointestinal, including pancreatitis; reproductive; endocrine; dermatologic; and respiratory. Increased water consumption and increased urination were also reported; however, these clinical signs weren't associated with a single body system.

Bromide toxicosis in dogs was most frequently associated with high serum bromide concentrations; however, toxicosis was seen at low concentrations in unusually sensitive dogs. Signs of more severe bromide toxicosis were similar across multiple species (such as rats, mice, dogs, cattle, horses, and people) and included depression, behavioral changes, ataxia, hind limb paresis, mydriasis, stupor, and coma.

The vast amount of literature available in the Public Master File provided a volume and variety of evidence to support the safety of KBr in dogs with idiopathic epilepsy.

Conclusions
Based on the information in the Public Master File and the data submitted by the sponsor for the approval of KBroVet®-CA1, FDA determined that the drug is safe and has a reasonable expectation of effectiveness when used according to the label.

Table of Contents

I. GENERAL INFORMATION

A. File Number

Application Number 141-544

B. Sponsor

Pegasus Laboratories, Inc.
8809 Ely Rd.
Pensacola, FL 32514

Drug Labeler Code: 055246

C. Proprietary Name

KBroVet®-CA1

D. Drug Product Established Name

Potassium bromide chewable tablets

E. Pharmacological Category

Antiepileptic

F. Dosage Form

Chewable tablets

G. Amount of Active Ingredient

250 or 500 mg per tablet

H. How Supplied

Tablets are packaged in bottles containing 60 or 180 tablets.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The total recommended daily dosage range for oral administration is 25-68 mg/kg (11-31 mg/lb) of body weight once daily. The dosage of KBroVet®-CA1 should be adjusted based on monitoring of clinical response of the individual patient. KBroVet®-CA1 may be dosed with or without food. Use of an initial loading dosage regimen may be considered on an individual patient basis, balancing the time required to achieve a therapeutic response while minimizing side effects.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

KBroVet®-CA1 (potassium bromide chewable tablets) are indicated for the control of seizures associated with idiopathic epilepsy in dogs.

II. EFFECTIVENESS

Conditional Dose: The conditional dose for the indication "for the control of seizures associated with idiopathic epilepsy in dogs" is 25-68 mg/kg (11-31 mg/lb) once daily. Use of an initial loading dosage regimen may be considered on an individual patient basis, balancing the time required to achieve a therapeutic response while minimizing side effects.

The data from two retrospective studies support dosage characterization and demonstrate reasonable expectation of effectiveness. The safety data and the data to demonstrate reasonable expectation of effectiveness provide support for this conditional use.

A. Dosage Characterization

The dose of KBroVet-CA1 administered orally once daily at 25-68 mg/kg (11-31 mg/lb) is based on a retrospective dose determination study.

Title: A Retrospective Evaluation of the Total Daily Oral Dose Range of Potassium Bromide to Achieve Serum Bromide Concentrations (Approaching Steady-State Conditions) that are within 10% of the Published Therapeutic Range in Dogs with Idiopathic Epilepsy. (Study No. PLI-CL017)

This retrospective evaluation was conducted to determine the total daily oral dose range of potassium bromide (KBr) necessary to achieve serum bromide concentrations (approaching steady-state conditions) that are within 10% of the published therapeutic range in dogs with idiopathic epilepsy. This evaluation did not involve prospective dosing or any assessment of patient response to treatment outcome. This evaluation considered client-owned dogs previously administered KBr in veterinary practice for management of canine idiopathic epilepsy as cases of record. To be included as an evaluable case, the dog had to be administered only KBr to control the seizures associated with idiopathic epilepsy. A database comprising information from these cases was generated by the Clinical Pharmacology Laboratory (CPL) in the College of Veterinary Medicine at Auburn University (Auburn, Alabama) during the course of routine blood sample submission from practicing veterinarians. The samples were analyzed to quantify serum bromide concentrations (SBC) for the purpose of therapeutic drug monitoring (TDM).

A total of 284 dogs in the database met the eligibility criteria for evaluation. The mean total daily oral dose of KBr was 46.4 (± 21.9) mg/kg. The mean dose duration was 187 (± 177) days and the median dose duration was 120 days (45-1,260 days). The most common dosing interval was twice daily (65.1% of the animals); the remaining animals were dosed once daily. The mean SBC resulting from the indicated KBr doses, duration, and intervals was 1.51 (± 0.5) mg/mL (range 0.8-3.1 mg/mL). The published therapeutic range for KBr for treating dogs with idiopathic epilepsy is (≥0.8 and ≤3.5 mg/mL).[1,2]

Based on upper and lower 95% confidence limits for the case population, the total daily oral dose range was 43.8-48.9 mg KBr per kg bodyweight. From this analysis the mean total daily oral dose was 46.4 (± 21.9) mg/kg; the dose range with one standard deviation was 24.5-68.3 mg/kg. These results describe the total daily oral dose of potassium bromide concentrations within 10% of the published therapeutic range for dogs with idiopathic epilepsy.

B. Reasonable Expectation of Effectiveness

Reasonable expectation of effectiveness for potassium bromide for the control of seizures associated with idiopathic epilepsy in dogs is based on the results of a retrospective, pilot field study (Study No. PLI-CL008).

Title: A Retrospective Pilot Study of the Effectiveness of Oral Potassium Bromide for the Control of Seizures Associated with Idiopathic Epilepsy in Dogs, PLI-CL008.

Study Dates: January 2005 to August 2010

Study Location: Auburn, AL

Study Design:

Objective: Retrospective evaluation of medical records of client-owned dogs previously treated with KBr for management of canine idiopathic epilepsy to characterize dose of KBr when administered orally for the control of seizures in dogs with idiopathic epilepsy

Study Animals: A programmatic query of the Clinical Pharmacology Laboratory (CPL) database at the College of Veterinary Medicine at Auburn University was implemented as the first step to identify a listing of veterinarians with dogs administered KBr intended to comprise the pilot therapeutic drug monitoring (TDM) database for this retrospective evaluation. To be included as an evaluable case, the dog had to be administered only KBr to control the seizures associated with idiopathic epilepsy. The target goal of this query was to identify an approximate total of 30-50 evaluable cases.

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[1] Boothe DM. Anticonvulsant and other neurologic therapies. In: Boothe DM, Ed. Small Animal clinical pharmacology and therapeutics. Philadelphia: WB Saunders Co.,2001; 431-456
[2] Dewey CW. Anticonvulsant therapy in dogs and cats. Vet Clin North Am Small Anim Pract 2006; 36:1107-1127.

Experimental Design: Retrospective evaluation of medical records of client-owned dogs previously treated with KBr for management of canine idiopathic epilepsy.

Drug Administration: Immediate-release oral KBr formulated or compounded as a tablet, chewable tablet, capsule, liquid, or sprinkle granules. There were no specified dosage requirements in the retrospective study protocol, but at the time of sentinel sample submission for KBr blood levels, the dog must have received the same total daily dose of KBr for a minimum of 60 days (the intention to approach steady state dosing conditions). In order to meet the inclusion criteria of the study, the dog must have had a serum bromide concentration ≥0.8 and ≤3.5 mg/mL.

Measurements and Observations: Seizure count, seizure event days, and seizure severity were assessed. Changes in seizure counts, seizure event days per month, and seizure severity scores were tabulated for eligible cases, comparing the 30 day period before initial treatment with KBr and the 30 day period of steady state KBr dosing. Contrasts were calculated for each variable within each case by subtraction of pre-treatment and steady state treatment phase responses.

In order to be counted as a treatment success, individual cases were required to meet all three of the following criteria:

1. Seizure count success: Seizure count within an individual case was required to decrease by 50% or greater in order for the case to be classified as a seizure count success (seizure count in the 30 days before initial treatment with KBr compared to seizure count in the 30 days before sentinel sample submission).
2. Seizure event day count success: Seizure event days per month for an individual case was required to decrease by 50% or greater in order for the case to be classified as a seizure event day count success.
3. Seizure severity score success: Severity score for an individual case was required to not increase for the case to be classified as a success for seizure severity.

Statistical Methods: Descriptive statistics were used to characterize effectiveness outcome variables, clinical findings, and adverse events.

Results: Case distribution, based on the included case medical records, spanned a 5.7 year period. A total of 189 cases were identified in the initial query, and of those, an initial pool of 97 cases was identified for potential data acquisition. Of those 97 cases, 46 cases were excluded from evaluation due to a lack of medical record data, inadequate diagnosis, or lack of veterinarian response to further queries. Thus, 51 of the 97 cases were further evaluated for study inclusion using the protocol-specified criteria. Of these 51 evaluable cases, 27 were determined as valid for safety and effectiveness data and 24 were determined to be valid for only safety data.

Case Distribution and Demographics: The 51 cases considered eligible for evaluation were from 18 different veterinary clinics. Contributed cases per veterinarian ranged from 1 to 10 dogs. Case distribution by year ranged from

2005 to 2010, with the majority of the 51 cases having been diagnosed and treated between 2006 and 2008. The majority of the 51 cases were male dogs (approximately 61%). Of the 51 cases, the mean age of onset of epilepsy was 2.1 years, the mean age of initiating KBr treatment was 2.4 years, and the mean age at the time of sentinel sample submission was approximately 3 years. Body weight data provided on 49 of the 51 cases showed a mean value of 23 kg, ranging approximately from 2 to 88 kg. The most commonly represented breeds were mixed (approximately 24%), followed by Golden Retriever and Labrador Retrievers, each comprising approximately 10% of the 51 cases. Case distribution by geographic location included 9 US states, with the majority from Texas and Maryland.

Dosage: The mean maintenance dose of the 51 cases evaluated for safety and effectiveness was 40.2 mg/kg/day, with a mean duration of dosing of 210 days. For the 27 cases comprising the effectiveness dataset, the mean maintenance dose was 37 mg/kg/day, with a mean duration of dosing of 286 days. Within the 27 cases evaluated for effectiveness, approximately 67% were dosed once daily and 33% were dosed twice daily. The majority of cases (63%) received KBr as a liquid dose form and approximately 31% received KBr in capsule form. Approximately 6% of the cases received KBr in tablet form.

Reasonable Expectation of Effectiveness: Of the 27 cases, 19 (70%) were defined as "success" and 8 (30%) were defined as "failures" based on seizure count results. Sixty seven percent (18/27) were defined as "success" and 9 (33%) were defined as "failures" based on seizure event day results. Seizure severity score decreased or did not change in 25 of the 27 cases evaluated for effectiveness. Overall, of the 27 dogs included in the effectiveness analysis, 18 (67%) were considered treatment successes and 9 (33%) were considered treatment failures.

Adverse Reactions: In the 51 cases included in the safety evaluation, increased appetite, weight gain, vomiting/regurgitation, and sedation were the most common adverse reactions documented in the 60 day period after start of KBr therapy.

Table II.1: Adverse Reactions Reported During Initial Dosing Phase (60 Day Period After Start of KBr Therapy)

Adverse Reaction	Number of Dogs with the Adverse Reaction
Increased Appetite	11
Weight Gain	8
Vomiting	5
Regurgitation	4
Sedation	3
Polydipsia	2
Ataxia	2
Polyuria	2
Weakness	2
Decreased Activity	1
Diarrhea	1
Disorientation	1
Lethargy	1
Partial Lack of Efficacy	1
Petit Mal Epilepsy	1
Seizure	1
Tiredness	1
Tremor	1

Adverse reactions were also documented during the 30 days prior to serum bromide sample submission. At the time of sample submission, the dog must have received the same total daily dose of KBr for a minimum of 60 days (expected steady state dosing conditions). Weight gain, weakness, drunken gait, increased water consumption, increased appetite, and sedation were the most common adverse reactions documented in the 30 day period before the sentinel bromide submission date.

Table II.2: Adverse Reactions Reported During Dosing Phase (30 Day Period of expected steady state dosing conditions)

Adverse Reaction	Number of Dogs with the Adverse Reaction
Weight Gain	7
Weakness	5
Ataxia	4
Increased Appetite	4
Polydipsia	3
Sedation	3
Diarrhea	2
Polyuria	2
Regurgitation	2
Vomiting	2
Decreased Appetite	1
Disorientation	1
Loose Stool	1
Panting	1
Tremors	1

Conclusions: The results of this retrospective study demonstrate a reasonable expectation of effectiveness for KBroVet®-CA1, at the total recommended oral daily dosage range of 25-68 mg/kg (11-31 mg/lb), for the control of seizures associated with idiopathic epilepsy. Sixty-seven percent of the cases in this retrospective study had a favorable overall response outcome. This study also supports the conclusion that KBr has an adequate safety profile in the target population.

III. TARGET ANIMAL SAFETY

The safety of KBroVet®-CA1 is supported by a Public Master File containing data describing the target animal safety of potassium bromide and the safety information from the pilot retrospective study, Study No. PLI-CL008, summarized above under Reasonable Expectation of Effectiveness.

A. Public Master File Reference – review of bromide safety

In September 2014, FDA CVM announced availability of a Public Master File containing data describing the target animal safety of potassium bromide to

support drug applications. This data is summarized in a published comprehensive review of published literature.[3]

Title: A systematic review of the safety of potassium bromide in dogs.

The objective of this systematic review was to critically evaluate and summarize the available information on the safety of potassium bromide in dogs. PubMed searches without date limitations were conducted with the terms "potassium bromide" and "sodium bromide" in December 2009 and October 2011. Additional articles were identified through examination of article reference lists and book chapters on seizures in dogs and pharmacology. Following this approach, the systematic review included 111 references reporting safety information relevant to potassium bromide published between 1938 and 2011.

Reversible neurologic signs were the most consistently reported toxicosis and were generally associated with adjunctive potassium bromide treatment or high serum bromide concentrations. Dermatologic and respiratory abnormalities were rare in dogs. Insufficient information was available to assess the effects of potassium bromide on behavior or to determine the incidence of vomiting, weight gain, polyphagia, pancreatitis, polyuria, polydipsia, or reproductive abnormalities associated with potassium bromide administration. Evidence suggested that administration of potassium bromide with food may alleviate gastrointestinal irritation and that monitoring for polyphagia, thyroid hormone abnormalities, and high serum bromide concentrations may be beneficial.

Results suggested that potassium bromide is not an appropriate choice for treatment of every dog with seizures and that veterinarians should tailor therapeutic regimens and clinical monitoring to each dog. Abrupt dietary changes or fluid therapy may compromise seizure control or increase the likelihood of adverse events.

Based on the reviewed articles, the most common adverse drug events reported were found in the neurologic (including behavioral), gastrointestinal (including pancreatitis), reproductive, endocrine, dermatologic, and respiratory systems. Polyuria and polydipsia were also present; however, they were not associated with a single body system.

Animals with decreased renal function may be predisposed to bromide toxicosis owing to a decreased ability to eliminate bromide as a result of reduced glomerular filtration rate.

Abrupt diet changes in dogs receiving KBr could either compromise seizure control or raise safety concerns.

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[3] Baird-Heinz HE, Van Schoick AL, Pelsor FR, Ranivand L, Hungerford LL. A systematic review of the safety of potassium bromide in dogs. J Am Vet Med Assoc. 2012 Mar 15;240 (6):705-15. DOI: 10.2460/javma.240.6.705.

Bromide toxicosis in dogs was most frequently associated with high serum bromide concentrations; however, authors have reported that toxicoses can be seen at low concentration in unusually sensitive dogs. One study found that most dogs that develop signs of toxicoses with bromide monotherapy had serum bromide concentrations in the range of 2.4 to 4 mg/mL, but this study also found that dogs were successfully treated without signs of toxicosis at serum concentrations as high as 4 to 4.8 mg/mL. Another publication reported clinical signs of toxicosis at serum bromide concentrations of approximately 4 mg/mL, but no signs of toxicoses at concentrations of 1.78 to 2.7 mg/mL. In a laboratory study, unspecified minimal signs of toxicosis were found in dogs administered a daily dose of 100 mg of NaBr/kg (45.5 mg/lb/d) for 6 weeks; mean serum concentration was 2.7 mg/mL.

It is important to monitor clinical signs of individual animals because effective and toxic serum bromide concentrations have been reported to differ between dogs and an overlap in toxic versus nontoxic serum concentrations has been demonstrated. In fact, the use of clinical signs to judge appropriateness of treatment may be more important than monitoring serum bromide concentration alone.

Signs of more severe bromide intoxication were similar across species (humans, rats, mice, dogs, cattle, and horses) and included signs of depression, behavioral changes, ataxia, hind limb paresis, mydriasis, stupor, and coma.

Skin lesions were rarely reported in experimental overdose studies or in summaries of clinical cases of bromide intoxication in dogs. When reported, skin lesions in dogs were described as nonsuppurative white macules with scales or as pustular dermatitis. Development of sterile nodular panniculitis has been reported in patients receiving potassium bromide. This adverse event, which also appears in human medicine, appears to be dose dependent, most likely to happen after an increase in dose, and clinical signs appear to resolve upon withdrawal of the drug.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food-producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to KBroVet®-CA1:

Not for human use.
Keep out of reach of children.
Consult a physician in case of accidental ingestion by humans.

VI. AGENCY CONCLUSIONS

The data submitted in support of this application satisfy the requirements of section 571(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The data demonstrate that KBroVet®-CA1, when used according to the label, is safe and has a reasonable expectation of effectiveness for the control of seizures associated with idiopathic epilepsy in dogs.

A. Conditional Approval Eligibility

In 2018, the legislation reauthorizing FDA's animal drug user fee program (Animal Drug User Fee Program, or ADUFA, IV) expanded the conditional approval pathway to allow certain additional new animal drugs that are not Minor Use/Minor Species (MUMS) drugs to be eligible for conditional approval. As provided in section 571(a)(1)(A)(ii) of the Food Drug and Cosmetic (FD&C) Act, as amended by ADUFA IV, to qualify for conditional approval, the non-MUMS new animal drug must meet the following two criteria:

1. The new animal drug is intended to treat a serious or life-threatening disease or condition OR addresses an unmet animal or human health need; AND
2. A demonstration of effectiveness would require a complex or particularly difficult study or studies.

KBroVet®-CA1 was determined to be eligible for conditional approval under these provisions because it controls a serious or life-threatening disease or condition, addresses an unmet animal health need, and the demonstration of effectiveness requires a complex or particularly difficult study or studies. The condition, idiopathic epilepsy in dogs, is a disease or condition associated with morbidity that has substantial impact on day-to-day functioning in the target animal. Therefore, the conditionally approved use addresses a serious or life-threatening disease or condition. The control of idiopathic epilepsy in dogs was also determined to be an unmet animal health need because there is no approved animal drug currently being marketed in the United States for this use in dogs. Finally, based on the unpredictability of the occurrence or outcome of the disease or condition, and the need for use of advanced or complicated tests to diagnose idiopathic epilepsy, it was determined that the demonstration of effectiveness requires a complex or particularly difficult study or studies.

B. Marketing Status

KBroVet®-CA1 is conditionally approved for one year from the date of approval and is annually renewable for up to four additional one-year terms.

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional veterinary expertise is required to diagnose idiopathic epilepsy and to monitor safe use of the product, including treatment of any adverse reactions.

C. Exclusivity

KBroVet®-CA1, as conditionally approved in our approval letter, does not qualify for exclusive marketing rights under section 573(c) of the FD&C Act because it is not a designated new animal drug under section 573(a) of the FD&C Act.

D. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.