

KBROVET[®] **(potassium bromide chewable tablets)**

Anti-epileptic for use in dogs only.

Approved by FDA under NADA #141-615.

CAUTION:

Federal law restricts this drug to use by or on the order of a licensed veterinarian. Use only as directed.

DESCRIPTION:

KBroVet are flavored chewable tablets that contain potassium bromide (KBr). KBr is an odorless, colorless crystal or white crystalline powder or white granular solid with a pungent bitter saline taste. The molar mass of KBr is 119.002 g/mol, with high solubility in water, glycerol and ethanol.

INDICATION:

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

DOSAGE AND ADMINISTRATION:

The total recommended daily dosage range for oral administration is 25 - 68 mg/kg (11-31 mg/lb) of body weight. The dosage of KBroVet should be adjusted based on monitoring of clinical response of the individual patient. KBroVet 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. Tablets should not be split.

CONTRAINDICATIONS:

KBroVet should not be used in animals with a history of sensitivity to bromide.

WARNINGS:

User Safety Warnings

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

Animal Safety Warnings

Not for use in cats.

Keep KBroVet in a secured location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

PRECAUTIONS:

Dogs receiving KBr should be carefully monitored when changing diets, administering chloride-containing IV fluids, and administering concurrent medications. Careful monitoring is important in dogs that have a condition that may cause difficulty maintaining electrolyte balance.

Dogs with decreased renal function may be predisposed to bromide toxicosis.

Some dogs may experience epileptic episodes that are unresponsive or refractory to KBr monotherapy and KBr alone may not be adequate treatment for every dog with idiopathic epilepsy (IE).

The safe use of KBroVet has not been evaluated in dogs that are intended for breeding, or that are pregnant or lactating. Reproductive effects of KBr have been reported in other species. The safe use of KBr in neonates and puppies has not been established.

ADVERSE REACTIONS:

In a retrospective study of 51 dogs diagnosed with IE and receiving KBr monotherapy to control seizures associated with IE, adverse reactions were documented for the initial 60 days of treatment (Table 1). Increased appetite, weight gain, vomiting/regurgitation and sedation were the most common clinical abnormalities documented in the 60-day period after start of KBr therapy.

Table 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 |
| Decreased Activity | 3 |
| Polydipsia | 2 |
| Ataxia | 2 |
| Polyuria | 2 |
| Weakness | 2 |
| Diarrhea | 1 |
| Disorientation | 1 |
| Partial Lack of Effectiveness | 1 |
| Petit Mal Epilepsy | 1 |
| Seizure | 1 |
| Tremors | 1 |

Adverse reactions were also documented for 30 days when KBr was at steady state (Table 2). Weight gain, weakness, ataxia, and increased appetite were the most common adverse reactions documented during this time period.

Table 2. Adverse Reactions Reported During Dosing Phase (KBr at Steady State)

| 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 |

In a second retrospective study, in which 46 dogs received KBr, safety data was collected for 60 days. There was a total of 33 adverse reactions considered related to KBr affecting 26/46 dogs. The most common adverse reactions were weight gain, vomiting, and sedation, and the other reported adverse reactions included polyuria, polydipsia, polyphagia, ataxia, and lethargy.

Adverse events associated with concurrent use of KBr with other antiepileptic drugs, such as phenobarbital, have been reported in literature. Neurologic signs were the most common adverse event, and other reported adverse events included sedation, irritability, restlessness, depression, behavioral changes, ataxia, hind limb paresis, mydriasis, stupor, and coma. The neurologic signs were reported to be reversible if treatment was stopped.

CONTACT INFORMATION:

For a copy of the Safety Data Sheet (SDS) or to report suspected adverse drug events, contact Pegasus Laboratories at 1-800-874-9764. For additional information reporting adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY:

Mechanism of action: KBr is a halide salt that is thought to exert its antiepileptic activity by passing through neuronal chloride ion channels, thereby hyperpolarizing neuronal membranes, raising the seizure threshold, and stabilizing neurons against excitatory input from epileptic foci.

Pharmacokinetics: The pharmacokinetics of a multi-dose regimen of administration in normal dogs have been evaluated as described in a comprehensive literature review. In one study, KBr was administered at 30 mg/kg orally every 12 hrs for a period of 115 days. Serum, urine, and cerebrospinal fluid (CSF) bromide concentrations were measured at the onset of dosing, during the accumulation phase, at steady-state, and after a subsequent dose adjustment.

Median elimination half-life and steady-state serum concentration were 15.2 days and 245 mg/dL (2.45 mg/mL), respectively. Apparent total body clearance was 16.4 mL/day/kg and volume of distribution was 0.40 L/kg. The CSF:serum bromide ratio at steady state was 0.77.

Bromide distributes into the CSF and interstitial tissues of the brain and is actively transported out of the CNS via the choroid plexus. At pharmacological doses, the active transport mechanism is overwhelmed and bromide accumulates in the brain and CSF. Bromide is not metabolized by the liver and is eliminated unchanged, primarily by renal clearance. Increased dietary consumption of chloride can promote loss of bromide in the urine, leading to a lowering of serum bromide concentrations. Decreased chloride consumption will promote increased renal reabsorption of bromide, causing an increase in bromide elimination half-life in dogs.

EFFECTIVENESS:

A retrospective study involving review of case records of 51 client-owned dogs was conducted to evaluate the effectiveness of KBr in dogs. This study evaluated case records of dogs 0.5 to 5 years of age administered KBr monotherapy to control seizures associated with IE and for which blood samples had been analyzed to quantify serum bromide concentrations for the purpose of therapeutic drug monitoring.

Seizure counts, seizure count changes, seizure event days per month and seizure severity scores were tabulated for eligible cases, comparing the 30-day period before initial treatment with KBr to a 30-

day period of steady state KBr dosing. Seizure count for an individual case was required to decrease by 50% or greater in order for the case to be classified as a seizure count success. Similarly, reduction in the number of seizure event days per month by $\geq 50\%$ was required for the case to be classified as a seizure event day count success. Of the 51 evaluable cases, 27 were included in the effectiveness evaluation and all 51 were included for safety.

Of the 27 cases evaluated for effectiveness, 19 (70%) met the success criteria and 8 (30%) were failures based on seizure count results. Eighteen (67%) met the success criteria and 9 (33%) were 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.

In a second retrospective study, a total of 287 candidate cases were identified, 46 of which were evaluated for effectiveness. This study evaluated case records of dogs 0.5 to 5 years of age administered KBr monotherapy at a dose between 25 and 68 mg/kg/day to control seizures associated with IE. The majority of dogs were female (52%) with a mean body weight of 20.2 (standard deviation (SD) 12.8) kg and a range of 3 to 44 kg. The median age at IE diagnosis and start of KBr therapy were 3 (0.7, 5.3), and 3.2 (0.7, 5.6) years, respectively. Mixed breed (22%) and Labrador Retriever (11%) were the most common breeds. Effectiveness was based on seizure frequency during the 30-day baseline and treatment response periods. Seizure frequency was expressed as the number of seizures occurring in a 30-day period. Between baseline and the 30-day post treatment evaluation, 40 of the 46 cases experienced at least a 50% reduction in seizure frequency.

Because of their retrospective nature, neither of the studies described above were controlled. A placebo response rate in dogs with IE has been reported to be 29%.¹

The overall evidence, based on the results of the two retrospective studies, four decades of reported use for management in veterinary medicine, as well as published literature supports the conclusion that KBroVet is effective for the control of seizures associated with IE in dogs.

TARGET ANIMAL SAFETY:

Safety was assessed in a systematic review of literature and two retrospective field studies. Reversible neurologic signs were the most consistently reported adverse effect and were generally associated with add-on KBr treatment or high serum bromide concentrations. Adverse effects were also seen in some dogs with low serum bromide concentrations. Dermatologic and respiratory abnormalities were rare in dogs. Evidence suggests that administration of KBr with food may alleviate gastrointestinal irritation and that monitoring for polyphagia, thyroid hormone abnormalities, and high serum bromide concentrations may be beneficial.

In dogs, ataxia, diarrhea, hematochezia, excessive salivation, shivering, skin lesions, stupor progressing to coma and death have been reported with a dose of 200 to 500 mg/kg a day for 4 to 26 weeks.

HOW SUPPLIED:

KBroVet (potassium bromide chewable tablets) are flavored, non-scored tablets containing 250 mg or 500 mg of potassium bromide per tablet. KBroVet is packaged in bottles containing 60 or 180 tablets.

500 mg Tablet (60 ct) bottle
NDC 49427-398-48
250 mg Tablet (60 ct) bottle
NDC 49427-397-48
500 mg Tablet (180 ct) bottle
NDC 49427-398-50
250 mg Tablet (180 ct) bottle
NDC 49427-397-50

STORAGE CONDITIONS:

Store at controlled room temperature 20-25°C (68-77°F).

Keep out of reach of children and animals.

¹ Muñana KR, Zhang D, Patterson EE. Placebo effect in canine epilepsy trials. J Vet Intern Med. 2010 Jan-Feb;24(1):166-70.

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PHARMACAL

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