LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

15 August 2022

SUMMARY OF PRODUCT CHARACTERISTICS

for

Vetbromide, tablets

0. D.SP.NO.
31888

1. NAME OF THE VETERINARY MEDICINAL PRODUCT
Vetbromide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains:

Active substance
600 mg potassium bromide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablets

White, round tablet with 2 score-lines on each side.
The tablet can be divided into 2 or 4 equal parts.

4. CLINICAL PARTICULARS

4.1 Target species
Dog

4.2 Indications for use, specifying the target species
An antiepileptic agent for use in the control of idiopathic epileptic seizures, either as a single agent or as an adjunct to phenobarbital in the control of refractory cases of idiopathic epilepsy.

4.3 Contraindications
Do not use in known cases of hypersensitivity to the active substance, or to any of the excipients.
Do not use in dogs with severe renal insufficiency.

4.4 Special warnings for each target species

The concentration of bromide in serum, the clinical response and the therapeutic effect of administration of the product may vary between individuals (see section 4.9). The presence of cluster seizures/status epilepticus, due to the severity of the seizure activity, is often associated with poor response to anti-epileptic treatment. In these cases, remission (seizure freedom) may be difficult to achieve.
For dogs with normal hepatic function, phenobarbital is generally considered the first-choice antiepileptic drug. However, potassium bromide can be recommended as alternative, especially in dogs with hepatic dysfunction or in dogs with concurrent disorders requiring life-long administration of potentially hepatotoxic medications, since potassium bromide is not metabolised in the liver (see section 5.2).
A high chloride intake can increase the elimination of bromide (see section 4.8). An increase in the dog's salt intake may require an adjustment in bromide dose. The salt content of a dog's diet during the treatment period should be maintained at a stable level. It is advisable not to change the dog's diet during therapy.

4.5 Special precautions for use

Special precautions for use in animals

Do not abruptly discontinue therapy as this may precipitate seizures.
This product should be used with caution in dogs with mild or moderate renal insufficiency, since excretion of bromide is reduced (see also section 4.3). To prevent bromide accumulation and a relative overdose of bromide (see 4.10), administer a reduced dose and monitor the serum bromide concentration closely (see 4.9).
A reduction in chloride intake (low sodium diet) can increase the likelihood of adverse reactions or bromide intoxication (see section 4.8 and 4.10).
Close monitoring for adverse reactions is advisable at higher serum bromide concentrations.
Administration on an empty stomach may induce vomiting.
Dogs weighing less than 10 kg cannot be accurately dosed with the recommended starting dose for adjunctive treatment of 15 mg/kg twice daily, as the minimum dose achievable by division of the Vetbromide 600 mg tablet is 150 mg (see section 4.9).

Special precautions to be taken by the person administering the veterinary medicinal product to animals

This product may cause eye-irritation. Avoid hand-to-eye contact. If the product comes into contact with the eyes, rinse immediately and thoroughly with clean water.
This product may be harmful upon ingestion, and cause adverse effects such as nausea and vomiting. Avoid oral ingestion including hand-to-mouth contact. To avoid accidental ingestion, particularly by a child, unused tablet parts should be returned to the open blister space and inserted back into the carton. Store in a closed cabinet. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
Wash hands thoroughly, immediately after breaking or handling tablets.

<u>To the physician</u>
An intravenous administration of isotonic sodium chloride (0.9%) will rapidly eliminate bromide ions in humans.

4.6 Adverse reactions (frequency and seriousness)

The most commonly reported adverse reactions are
- polyphagia, with or without weight gain (very common),
- neurologic signs: Ataxia, sedation, hind limb weakness (very common),
- polydipsia (very common), with or without polyuria,
- gastrointestinal disorders: Loose stools or diarrhoea, vomiting (very common),
- behavioural changes: Depression/ apathy, hyperexcitability, aggression (common),
- abnormal snoring (common),
- cough (common),
- loss of appetite (common),
- urinary incontinence and/or nocturnal urination (common)
- skin disorders (uncommon).

These adverse reactions may disappear after the first stage of treatment but may also persist in dogs on higher doses of therapy. In these cases, symptoms usually disappear following a reduction in dose. If the dog appears too sedated, assess the serum concentrations of bromide and, if applicable, phenobarbital to determine whether the dose of either should be reduced.
If potassium bromide dose is reduced, serum bromide concentrations should be monitored in order to ensure that they fall within the therapeutic range.

In some cases, an increase in serum cPLi after treatment with KBr was observed. Although pancreatitis has been suggested to occur in association with the administration of bromide and/or phenobarbital, there is no conclusive evidence of a direct causal relationship between bromide administration and the development of pancreatitis in dogs.
Treating dogs with potassium bromide can cause a decrease in T4 plasma concentration, although this is not necessarily clinically relevant.

The frequency of adverse reactions is defined using the following convention
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or laying

Studies in laboratory animals have not revealed any adverse effects of potassium bromide on reproduction at non-maternotoxic doses. The safety of the veterinary medicinal product has not been established during pregnancy and lactation in dogs. Use only according to the benefit/risk assessment by the responsible veterinarian.
Potassium bromide crosses the placental barrier. Since bromide may be excreted into milk, monitor suckling puppies for somnolence/sedative effects; if necessary, consider early weaning, or an artificial suckling method.

4.8 Interaction with other medicinal products and other forms of interaction

Due to the competition between chloride ions and bromide ions for reabsorption by the kidneys, any major change in chloride intake can modify serum bromide concentrations which are directly correlated to treatment efficacy and the occurrence of adverse reactions. A reduction in chloride intake (low sodium diet) can cause a rise in serum bromide levels

and increase the likelihood of bromide intoxication (see section 4.10). An increase in chloride intake (high salt diet) can cause a fall in serum bromide levels which could lead to seizures. Where possible, the diet of treated dogs should therefore not be altered. Seek veterinary advice before making any change to the dog's diet.

On biochemistry profiles serum chloride concentrations are often falsely elevated because the assays cannot distinguish between chloride and bromide ions.

Loop diuretics such as furosemide can increase bromide excretion and lower the efficacy of the treatment (risk of recurrence of seizures) if the dose is not adjusted.

Administration of fluids or drug formulations containing chloride can lower serum bromide concentrations.

Bromide is synergistic with other GABA-ergic drugs such as phenobarbital.

4.9 Amounts to be administered and route of administration

Oral use.
Administer twice daily with food in order to reduce the risk of gastrointestinal irritation.

In dogs with severe and frequent seizures or when a dog is being switched rapidly from phenobarbital to potassium bromide, a loading dose of 60 mg/kg bodyweight twice daily, for 5 days (equivalent to a total daily dose of 120 mg/kg) can be administered in order to quickly reach therapeutic serum concentrations.

The maintenance dose should be titrated to the individual dog as the required dosage and therapeutic serum bromide concentration may vary between animals and depends on the nature and severity of the underlying disease.

Monotherapy
The recommended starting dose is 30 mg/kg bodyweight twice daily (equivalent to a total daily dose of 60 mg/kg).

Adjunctive treatment, in combination with phenobarbital
The recommended starting dose is 15 mg/kg bodyweight twice daily (equivalent to a total daily dose of 30 mg/kg). Use in dogs with a bodyweight of less than 10 kg should be subject to a risk/benefit assessment, see section 4.5.

At the beginning of treatment, bromide serum concentrations should be checked regularly, e.g. 1 week and 1 month after the loading period and three months after treatment initiation at maintenance dosage. Therapeutic serum levels vary between 1000 mg/L to 3000 mg/L when potassium bromide is used as monotherapy and between 800 mg/L and 2000 mg/L, when used as adjunctive treatment. Close monitoring for side effects is advisable, particularly when serum bromide concentrations have reached the upper limit of the therapeutic range for monotherapy.

It is recommended to administer at least half of the initial starting dose to dogs with mild or moderate renal insufficiency, with more frequent monitoring of serum bromide levels (see section 4.5).

If the clinical response is not satisfactory or if adverse reactions occur, the dose may be adjusted based on the dog's serum bromide levels. Serum concentrations should be measured after each dose adjustment once steady state serum levels have been reached (typically 3 months after a change), unless earlier evaluation is necessary. Long term monitoring of serum bromide concentrations should be performed as clinically justified by the individual case.

4.10 Overdose (symptoms, emergency procedures, antidotes)

Clinical signs of bromide toxicity (e.g. ataxia, somnolence) can occur in dogs with renal insufficiency or when a very high dose of bromide is administered. If overdose is suspected, the dosage should be reduced immediately, with close monitoring of serum bromide concentrations in order to establish an appropriate therapeutic concentration. Dose and serum bromide levels at which intolerance is observed vary between dogs. In cases of overdose requiring medical attention, administer 0.9 % sodium chloride solution intravenously to reduce serum bromide concentrations.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antiepileptics, other antiepileptics.
ATCvet-code: QN 03 AX 91.

5.1 Pharmacodynamic properties

Potassium bromide is a halide anticonvulsant. Bromide replaces chloride in all body fluids. It competes with chloride transport across nerve cell membranes and inhibits sodium transport and so causes membrane hyperpolarisation. This hyperpolarisation raises the seizure threshold and prevents the spread of epileptic discharges. Bromide has effects on active transport across ganglial cell membranes and affects passive movements of ions by competition with chloride for anion channels in post-synaptic membranes that are activated by inhibitory neurotransmitters. This potentiates the effect of GABA which results in a synergistic activity of bromide with other drugs that have GABA-ergic activity, such as phenobarbital.

5.2 Pharmacokinetic particulars

After oral administration, the potassium bromide salt dissociates and bromide ions are absorbed passively by the gastrointestinal tract. After absorption, the bromide ion rapidly and widely distributes, as does chloride, throughout the extra-cellular space and into cells. As the bromide level is increased in the body, the concentration of chloride is decreased in direct proportion to the increase in bromide.
The half-life can vary significantly with dietary chloride content, from approximately 14 days to more than 40 days. Due to this extremely long half-life, it can take several weeks/months to achieve steady state serum concentrations.
Bromide ions are excreted unchanged as the monovalent anion. Excretion of bromide is mainly via glomerular filtrations in the kidneys. The rate of elimination of bromide ions increases with chloride intake, as bromide competes with chloride for tubular reabsorption.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose, microcrystalline
Silica, colloidal anhydrous
Glycerol dibehenate
Magnesium stearate

6.2 Major incompatibilities

Not applicable.

6.3 Shelf-life

Packaged for sale: 4 years.

6.4 Special precautions for storage

Store below 30 °C.

After piercing a blister, replace unused tablet parts into the blister and place the blister back into the carton. Remaining tablet portions should be given at the next administration.

6.5 Nature and composition of immediate packaging

PVC/PVDC/Aluminium blister, in cardboard box.

Pack sizes
60 tablets (four blisters with 15 tablets each).
120 tablets (eight blisters with 15 tablets each).

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

DOMES PHARMA
3 rue André Citroën
63430 Pont-du-Château
Frankrig

8. MARKETING AUTHORISATION NUMBER(S)

63755

9. DATE OF FIRST AUTHORISATION

28 January 2021

10. DATE OF REVISION OF THE TEXT

15. August 2022

11. LEGAL STATUS

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