LIAVIUM™-CA1
(pregabalin chewable tablets)

For oral use in dogs only.
Analgesic

Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-606.

It is a violation of Federal law to use this product other than as directed in the labeling.

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

DESCRIPTION:
LIAVIUM™-CA1 (pregabalin chewable tablets) contains the active ingredient pregabalin.

LIAVIUM™-CA1 is available in 30 mg, 90 mg, and 180 mg tablet strengths. LIAVIUM™-CA1 30 mg and 180 mg tablets are off-white to light brown flecked tablets, plain on both sides. LIAVIUM™-CA1 90 mg are off-white to light brown flecked tablets, plain on one side with a break-line on the other side.

INDICATION:
LIAVIUM™-CA1 is indicated for the management of pain and clinical signs associated with Chiari-like malformation and syringomyelia in dogs.

DOSAGE AND ADMINISTRATION:
Administer LIAVIUM™-CA1 chewable tablets at 5–10 mg/kg orally twice daily. LIAVIUM™-CA1 should be administered with food. The 90 mg tablet is scored and may be split in half along the break-line. The 30 mg and 180 mg tablets should not be split.

Dogs under 3 kg cannot be accurately dosed with LIAVIUM™-CA1.

Pregabalin may be administered concurrently with a non-steroidal anti-inflammatory drug (NSAID).

CONTRAINDICATIONS:
Do not use in dogs with a known hypersensitivity to pregabalin.

WARNINGS:
Human User Safety Warnings:
Not for human use. Keep out of reach of children.

Take precautions to avoid accidental ingestion by children. Always store tablets in the original packaging and only remove the required number of tablets from the bottle at the time of dosing. Ensure that any tablets that are not eaten by the dog are disposed of immediately and carefully.

In case of accidental eye or mucosal contact, flush with water for 15 minutes. If wearing contact lenses, eyes should be rinsed first, then remove contact lenses and continue rinsing. In case of skin contact, wash with soap and water immediately.

Symptoms of exposure to pregabalin include dizziness, sleepiness, balance problems, blurred vision, weakness, dry mouth, difficulty with concentration or attention, and headache. Do not drive as sleepiness may occur.

In case of accidental ingestion, seek medical advice if symptoms occur. In case of ingestion by a child, seek medical attention immediately. Show the package insert or the label to the physician.

If the dog vomits after product administration, avoid skin contact with vomit and any tablet remnants, use impervious gloves during cleaning up and wash hands afterwards.

Women who are pregnant, who may become pregnant or are breastfeeding should take particular care to avoid contact with pregabalin.

People with known hypersensitivity to pregabalin should administer LIAVIUM™-CA1 with caution.

Drug Abuse, Misuse, Addiction, and Diversion:
Controlled Substance: LIAVIUM™-CA1 contains pregabalin, a Schedule V controlled substance.

Abuse: Abuse is defined as the intentional, non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Pregabalin is not known to be active at receptor sites associated with drugs of abuse. However, pregabalin is associated with drug liking and is known to be misused and abused in the community, particularly in combination with opioids. Consider the potential risks of misuse and abuse before prescribing this product. Signs of pregabalin misuse or abuse include drug seeking behavior.

LIAVIUM™-CA1 should be handled appropriately to minimize the risk of diversion, including restriction of access, the use of accounting procedures, and proper disposal methods, as appropriate to the clinical setting and as required by law.

Storage and Disposal: LIAVIUM™-CA1 is a Schedule V drug. Store in a locked cabinet according to federal and state controlled substance requirements and guidelines. Any unused or expired bottles must be destroyed by a reverse distributor. For further information, contact your local DEA field office or call PRN Pharmacal at 1-800-874-9764.

Information for Physician:
LIAVIUM™-CA1 contains pregabalin. In case of emergency, provide the treating physician with this package insert.

To obtain a copy of the Safety Data Sheet (SDS), contact PRN Pharmacal at 1-800-874-9764.

Animal Safety Warnings:
Keep LIAVIUM™-CA1 in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

PRECAUTIONS:
LIAVIUM™-CA1 has not been evaluated in dogs with renal disease. Pregabalin is excreted by the kidneys and an adjustment of the pregabalin dose in dogs with renal disease may be necessary.

LIAVIUM™-CA1 has not been evaluated in dogs that are pregnant, nursing or intended for breeding.

ADVERSE REACTIONS:
Based on publications in the scientific literature, the following adverse reactions are associated with administration of pregabalin in dogs:

General: somnolence, increased appetite, decreased activity, increased water intake, decreased body temperature or hypothermia

Neurologic: ataxia, sedation

Contact Information:
For technical assistance or to report suspected adverse drug experiences contact PRN Pharmacal at 1-800-874-9764. For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY:
Mechanism of action:
Pregabalin is a ligand of alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system. Pregabalin reduces the presynaptic calcium influx in neurons and there by the release of various neurotransmitters, including glutamate, norepinephrine, serotonin, dopamine, substance P and calcitonin gene-related peptide.

Pharmacokinetics:
The pharmacokinetics of LIAVIUM™-CA1 in dogs has not been evaluated. In the literature, it has been reported that following a single oral dose of pregabalin in dogs (n=6) at a dose range of 3.6 to 5.6 mg/kg (median 4.6 mg/kg), the median (range) elimination half-life was 6.9 (6.21-7.40) hours, the maximum plasma concentration (Cmax) was 7.15 (4.6-7.9) µg/mL, time to Cmax was 1.5 (1.0-4.0) hours, and the area under the

curve from zero to 36 hours was 81.8 (56.5-92.1) µg*hr/mL.

Reasonable Expectation of Effectiveness:
A reasonable expectation of effectiveness may be demonstrated based on evidence such as, but not limited to, pilot data in the target species or studies from published literature.

LIAVIUM™-CA1 is conditionally approved pending a full demonstration of effectiveness.

Additional information for Conditional Approvals can be found at www.fda.gov/animalca.

A reasonable expectation of effectiveness for LIAVIUM™-CA1 for the management of pain and clinical signs associated with Chiari-like malformation (CLM) and syringomyelia (SM) in dogs is based on a publication in the scientific literature.

The publication describes a masked, randomized, placebo-controlled, crossover design study that enrolled nine Cavalier King Charles Spaniels with CLM and SM (one dog had CLM only). All dogs received concurrent treatment with a nonsteroidal anti-inflammatory drug during the study. At Visit 1 (baseline), dogs were randomized to receive either pregabalin or placebo for 14 ± 4 days followed by a crossover to the alternate group at Visit 2 for 14 ± 4 days. Visit 3 occurred at the end of the second dosing phase. Dogs received a pregabalin oral solution at 5 mg/kg twice daily during the pregabalin phase. Effectiveness was based on a numerical rating scale (NRS) conducted daily by the dog owner and quantitative sensory testing (QST) conducted by the veterinarian at Visits 1, 2, and 3. The dog-owner NRS assessment included assessment of spontaneous vocalizations, phantom scratching episodes, and exercise impairment to determine the pain severity which was scored on a scale of 0–10 (0 = no pain, 10 = worst pain). The QST included stimuli threshold testing of skin on the neck, humerus, and tibia (all bilateral, total of six testing sites). The stimuli included tactile sensory thresholds and tactile allodynia (Von Frey filaments), mechanical threshold (algometer/pressure), heat threshold (thermal probe) and cold/cool latency (0 °C and 15 °C, thermal probe) assessments. One dog in the placebo group was removed from the study before the crossover due to a non-treatment related adverse event and not included in the results; eight dogs continued in the study and were treated. Blood and urine samples were collected at each visit for plasma creatinine, urinalysis, and urine specific gravity; the clinical pathology results were normal for all dogs at all visits. Results for the owner recorded NRS scores indicated that dogs were less painful during the pregabalin phase compared to the placebo phase and baseline. Pregabalin administration resulted in higher mechanical and heat thresholds, and longer cool/cold latency times on the neck and humeri compared to placebo and baseline.

TARGET ANIMAL SAFETY:
In a masked, controlled, laboratory study, 32 dogs (four/sex/group), aged 9-23 months and weighing 6.3-16 kg at study initiation, were administered LIAVIUM™-CA1 (pregabalin chewable tablets) at 0, 10, 30, and 50 mg/kg (0X, 1X, 3X, and 5X the maximum label dose) twice daily for 90 days. Dogs in the control group (0X) were sham dosed. Dogs in the LIAVIUM™-CA1 groups were dosed in a fed state.

Dogs were healthy based on physical examination and clinical pathology (hematology, serum chemistry, urinalysis, and coagulation times). There were no clinically relevant effects of administration of LIAVIUM™-CA1 on food consumption, heart rate, hematology variables, serum chemistry variables, coagulation times, electrocardiograms, necropsy, and histopathology. There was a dose dependent effect for lower body temperature or mild hypothermia in the 50 mg/kg group dogs. Dull mentation was observed in one 50 mg/kg group dog on Day 63 one hour after dosing. There were no other abnormal physical or neurological examination findings. Glycosuria without hyperglycemia occurred in one dog in the 10 mg/kg dose group, and two dogs each in the 30 mg/kg and 50 mg/kg dose groups.

HOW SUPPLIED:
LIAVIUM™-CA1 30 mg, 90 mg, and 180 mg chewable tablets are supplied in a white high density polyethylene container with a child resistant closure. Each bottle contains 60 tablets.

STORAGE INFORMATION:
Store at 20-25 ˚C (68-77 ˚F), excursions permitted between 15-30 ˚C (59-86 ˚F). Do not remove desiccant from bottle. Completely close bottle between uses. LIAVIUM™-CA1 is a Schedule V drug. Store in a locked cabinet according to federal and state controlled substance requirements/guidelines.

PRN®
PHARMACAL

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