MANAGEMENT OF MYXOMATOUS MITRAL VALVE DISEASE

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HEART MURMUR AUSCULTED ON EXAMINATION

- Determine intensity and location of murmur
- Perform thoracic radiography
  - Evaluate for evidence of hemodynamic changes
  - Measure VHS (±VLAS)
- Obtain blood pressure measurement
- Closely assess respiratory rate
- Obtain echocardiogram, if available
  - Identify cause of murmur, severity of cardiac chamber enlargement, and potential comorbidities
  - In adult small-breed dogs with a left-sided systolic murmur, if echocardiography is declined, a reasonable assumption can be made that mitral valve disease is the cause of the murmur
- Obtain NIBP
  - Identify if concurrent hypertension is present
  - Obtain a baseline value in asymptomatic pets

Are radiographic or echocardiographic changes present?

YES

- Is patient showing or has the patient ever shown clinical signs of cardiac failure?

YES

See Stage C, (Acute) next page

Stage B2

- If relying solely on radiographic evidence, the following criteria should be met before initiation of treatment:
  - Murmur intensity ≥3/6
  - VHS >11.5 (breed adjusted)
  - Consider pimobendan (0.25-0.3 mg/kg PO q12h)
  - Dietary modification
  - Recommend routine follow-up

NO

Stage B1

- No treatment necessary
- Obtain baseline blood work, blood pressure, and RRR
- Consider performing thoracic radiography and/or echocardiogram in 6 to 12 months
- Have pet owner monitor RRR at home using the Cardalis RRR app

NO

Stage B1

- No treatment necessary
- Obtain baseline blood work, blood pressure, and RRR
- Consider performing thoracic radiography and/or echocardiogram in 6 to 12 months
- Have pet owner monitor RRR at home using the Cardalis RRR app

For more detailed MMVD recommendations, please reference the ACVIM 2019 consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs.
Stage D

- Initiate treatment for refractory heart failure
  - Furosemide CRI (0.7-1 mg/kg/hr) until respiratory stress decreases
  - Consider torsemide if patient fails to respond to furosemide
  - Consider increasing pimobendan frequency to q8h
  - Consider more vigorous afterload reduction (nitroprusside CRI 1-15 µg/kg/min; nitroglycerin paste) for poorly responsive pulmonary edema
  - Consider dobutamine CRI 2.5-10 µg/kg/min to improve left ventricular function
  - Recommend specialist referral for more intensive care

Stage C (Chronic)

- Initiate chronic management of heart disease (ie, quad therapy)
  - Continue furosemide (2 mg/kg PO q12h) to effect
  - Continue pimobendan therapy (0.25-0.3 mg/kg PO q12h)
  - Initiate environmental changes (eg, weight loss, dietary modification, monitoring resting respiratory rate)
  - Initiate CARDALIS™ (spironolactone and benazepril hydrochloride chewable tablets) for complete RAAS blockade
    - Once-daily dosing has been shown to improve compliance
    - Highly palatable chewable tablet
  - Recheck renal values and electrolytes 3-14 days after initiating treatment
  - Have pet owner monitor RRR at home using the Cardalis RRR app

Stage C (Acute)

- Obtain minimum database (ie, CBC, serum chemistry), blood pressure, radiographs to assess for pulmonary edema, and urinalysis
- Initiate treatment for acute heart failure, including the following hospital-based treatments, as needed
  - Furosemide (2 mg/kg IV or IM q12h) until RRR and effort are improved or a total of 8 mg/kg is reached over 4 hours
  - Oxygen therapy, if needed
  - Pimobendan (0.25-0.3 mg/kg PO q12h)
  - Abdominocentesis or thoracocentesis if effusion is present
  - Sedation if patient is anxious due to dyspnea
  - Ensure appropriate nursing care (eg, access to water, temperature and humidity control while receiving oxygen, sternal body position)

References


CARDALIS™ is indicated with concurrent therapy (eg, furosemide) for the management of clinical signs of mild, moderate, or severe congestive heart failure in dogs due to atrioventricular valvular insufficiency (AVVI).

CARDALIS™ trademark is the property of Ceva Santé Animale S.A. The CARDALIS logo is a registered trademark of Ceva Santé Animale S.A.

IMPORTANT SAFETY INFORMATION

Do not administer in conjunction with non-steroidal anti-inflammatory drugs (NSAIDs) in dogs with renal insufficiency. Do not use in dogs with hypoadrenocorticism (Addison’s disease), hyperkalemia or hyponatremia. Do not use in dogs with known hypersensitivity to ACE inhibitors or spironolactone. The safety and effectiveness of concurrent therapy of Cardalis™ with pimobendan has not been evaluated. The safety of Cardalis™ has not been evaluated in pregnant, lactating, breeding, or growing dogs. Cardalis™ administration should begin after pulmonary edema is stabilized. Regular monitoring of renal function and serum potassium levels is recommended. Common side effects from a field study include anorexia, vomiting, lethargy, diarrhea and renal insufficiency.

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CHF = congestive heart failure
NBIP = noninvasive blood pressure
RRR = resting respiratory rate
VHS = vertebral heart scale
VLAS = vertebral left atrial size

Scan here for product information
Cardiac drug for oral use in dogs only
Approved by FDA under NADA # 141-538

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description: CARDALIS™ (spironolactone and benazepril hydrochloride chewable tablets) for dogs contains two active ingredients, spironolactone and benazepril hydrochloride, in a fixed ratio of 8:1 respectively. CARDALIS is supplied as oblong high scored flavellaw tablets in three sizes: 20 mg spironolactone and 2.5 mg benazepril hydrochloride, 40 mg spironolactone and 5 mg benazepril hydrochloride, and 80 mg spironolactone and 10 mg benazepril hydrochloride. Contraindications: Do not administer CARDALIS to dogs with known hypersensitivity to active ingredients or excipients. Dosage and Administration: CARDALIS should be administered orally once daily. The dosage of CARDALIS can be adjusted by titration to the minimum effective dose that will control the clinical signs of heart failure. Do not exceed the maximum recommended daily dose for individual dogs. Spironolactone, and its active metabolites, act as specific aldosterone antagonists. Spironolactone empirical formula is C24H32O4S and the molecular weight is 416.57. The chemical name is 21-hydroxy-7a-metopio-1,2,3,4,5-tetrahydro-2-oxo-1H-naphtho[2,3-d]imidazole-1-carboxyl acid lactate anhydride and the structural formula is shown below:

Spironolactone is a prodrug which, after absorption from the gastrointestinal tract, is rapidly converted by nonspecific carboxyl esterases, mainly in the liver, into its active metabolite benzbromarone. Benazepril is itself poorly absorbed from the gastrointestinal tract and the overall bioavailability of benazepril is about 10-20%. CARDALIS administration should begin after pulmonary edema is stabilized. CARDALIS should be administered orally once daily. The dosage of CARDALIS can be adjusted by titration to the minimum effective dose that will control the clinical signs of heart failure. Do not exceed the maximum recommended daily dose for individual dogs.

Contraindications: Do not administer CARDALIS in combination with non-steroidal anti-inflammatory drugs (NSAID) in dogs with renal insufficiency. Do not administer CARDALIS to dogs with hepatic dysfunction.

Benazepril hydrochloride is a prodrug which, after absorption from the gastrointestinal tract, is rapidly converted by nonspecific carboxyl esterases, mainly in the liver, into its active metabolite 7-α-thiomethyl-spironolactone. Spironolactone absorption is proportional at steady-state. There was no accumulation with repeated benazeprilat exposures; canrenone accumulation was 30%. Systemic exposure to the active metabolites of spironolactone (canrenone and 7-α-thiomethyl-spironolactone) and benazepril (benazeprilat) was dose proportional at steady-state. There was no accumulation with repeated benazeprilat exposures; canrenone accumulation was 30%. Systemic exposure to the active metabolites of spironolactone (canrenone and 7-α-thiomethyl-spironolactone) and benazepril (benazeprilat) was dose proportional at steady-state. Spironolactone and benazepril undergo extensive hepatic biotransformation. Care should be taken when using CARDALIS in dogs with hepatic dysfunction.

The safety of CARDALIS has not been evaluated in growing dogs. Spironolactone has an antiandrogenic effect and should be used with caution in growing dogs. The safety of CARDALIS has not been established in pregnant, lactating or breeding dogs.

Adverse Reactions: A U.S. clinical study comprised of a 360-day treatment period evaluated the safety and effectiveness of CARDALIS compared to benazepril hydrochloride in 56 client-owned dogs with left-sided heart failure (LHF). Table 1 summarizes the adverse reactions not directly related to the progression of disease that occurred in greater than 5% of the dogs treated with CARDALIS.

The following adverse events were seen in less than 5% of the study animals, in decreasing order: urine abnormalities, fluid in abdomen, ataxia, weight loss, degenerative tract disorder, hypertension, electrolyte disorder, bronchitis, and hyperactivity.

Renal insufficiency was reported more frequently in dogs treated with CARDALIS. This finding may be also attributed to the concurrent administration of furosamide. The clinical pathology parameters associated with renal function were not statistically different between the treatment groups. The incidence of death, including euthanasia and sudden death, was similar in dogs treated with CARDALIS or benazepril hydrochloride. In most cases, death was attributable to the progression of heart disease or the clinical signs associated with congestive heart failure. Deaths of unknown cause were not recorded. Serum magnesium and potassium values were significantly higher in the CARDALIS group, although the mean values remained within the reference range and did not change significantly over time. These electrolyte changes are consistent with the potassium-sparing properties of spironolactone. One dog dosed with CARDALIS was removed from the study due to development hyperkalemia. Contact Information: To report suspected adverse drug events or to request a copy of the Safety Data Sheet (SDS), please call Ceva Animal Health USA at 1-800-999-0279.

Clinical Pharmacology: Mechanism of Action: The main pharmacological target of spironolactone and benazepril is the renin-angiotensin-aldosterone system (RAAS) at different levels in the cascade. Spironolactone and its active metabolites (including 7-α-thiomethylspironolactone and canrenone) act as specific antagonists of aldosterone (regardless of the source) by binding competitively to mineralocorticoid receptors located in the kidney, heart and blood vessels.

Spironolactone is a prodrug hydrolyzed in vivo into its active metabolite, benzbromarone. Benazepril is a highly potent and selective inhibitor of angiotensin-converting enzyme (ACE), thus preventing the conversion of inactive angiotensin I to active angiotensin II. This prevents deleterious effects of deactivation and aldosterone release, including sodium and water retention, and vascular and myocardial remodelling. However, aldosterone release is not fully controlled by ACE inhibitors because angiotensin II is also produced by non-ACE pathways. Therefore, concurrent use of the aldosterone antagonist spironolactone and the ACE inhibitor benazepril hydrochloride inhibits both ACE and non-ACE pathways.

Pharmacokinetics: Spironolactone is rapidly and extensively metabolized in humans and experimental animals, with species differences in the metabolism and disposition. Spironolactone is metabolized by microsomal cytochrome P450 enzymes to a primary metabolite, canrenone, and a secondary metabolite, 7-α-thiomethylspironolactone (TMS), which are used as markers for spironolactone in dog plasma. Systemic exposure to both metabolites was comparable when spironolactone was administered alone or in association with benazepril in dogs. Spironolactone absorption is affected by food and the dose should be administered consistently in fed conditions. Maximum systemic exposure to canrenone was observed at 4 hours. After oral administration of radiolabeled spironolactone to the dogs, 70% of the dose is recovered in feces and 20% in the urine. After multiple oral doses of 2.5 mg of spironolactone in association with 2.5 mg of benazepril in dogs (n=8, 9 male and 9 female) for 10 consecutive days (steady state), no accumulation was observed. Treatment failure was defined as cardiac death or euthanasia (including death of unknown cause), recurrence or worsening of pulmonary edema, newly documented cardiogenic ascites, or clinical signs of congestive heart failure requiring administration of a furosemide dosage higher than 8 mg/kg/day. Failure rates at study Days 30, 90, 180, and 270 were also evaluated as secondary outcomes. The rate of failure in the CARDALIS group estimated from the model was statistically different (P = 0.0433) and numerically lower than that of the benazepril hydrochloride alone (active control).

Effects: The effectiveness of CARDALIS was evaluated in a well controlled U.S. multi-center, masked, randomized, 360-day field study in dogs with heart failure. The study evaluated the effectiveness of CARDALIS in dogs diagnosed with congestive heart failure caused by left-sided heart failure compared to benazepril hydrochloride alone (active control).

The data were analyzed using analysis of variance and Tukey’s multiple comparison test. The effectiveness of CARDALIS was evaluated in a well controlled U.S. multi-center, masked, randomized, 360-day field study in dogs with heart failure. The data were analyzed using analysis of variance and Tukey’s multiple comparison test.

Further, the rate of failure in the CARDALIS group was significantly lower than the group administered benazepril hydrochloride alone at all evaluation periods prior study Day 30. The dogs in the CARDALIS group exhibited a longer median time-to-failure when compared to the control group. The rate of treatment failure was defined as cardiac death or euthanasia (including death of unknown cause), recurrence or worsening of pulmonary edema, newly documented cardiogenic ascites, or clinical signs of congestive heart failure requiring administration of a furosemide dosage higher than 8 mg/kg/day. Failure rates at study Days 30, 90, 180, and 270 were also evaluated as secondary outcomes. The rate of failure in the CARDALIS group estimated from the model was statistically different (P = 0.0433) and numerically lower than that of the benazepril hydrochloride alone (active control).

Table 1: Adverse Reactions Occurring in ≥ 5% of the CARDALIS Treated Dogs

Table 2: Mean Pharmacokinetic Parameters for Canrenone and TMS on Day 10

Table 3: Mean Pharmacokinetic Parameters for Benazeprilat on Day 10

Table 4: Treatment Failure Rates by Treatment Group (Least Squares Means)

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