

Date of Approval: July 27, 2020

# FREEDOM OF INFORMATION SUMMARY

## ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-538

Cardalis™

spironolactone and benazepril hydrochloride chewable tablets

Dogs

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

Sponsored by:

Ceva Sante Animale

## Executive Summary

Cardalis™ (spironolactone and benazepril hydrochloride chewable tablets) is approved for use with concurrent therapy (e.g. furosemide, etc.) for the management of clinical signs of mild, moderate, or severe congestive heart failure in dogs due to atrioventricular valvular insufficiency (AVVI).

Spironolactone is an aldosterone antagonist and benazepril hydrochloride is an angiotensin-converting enzyme (ACE) inhibitor.

<b>Proprietary Name</b>	<b>Established Name</b>	<b>Application Type and Number</b>	<b>Sponsor</b>
Cardalis™	spironolactone and benazepril hydrochloride chewable tablets	<a href="#">New Animal Drug Application</a> (NADA) 141-538	Ceva Sante Animale

## Safety and Effectiveness

The sponsor conducted a 12-month field safety and effectiveness study comparing Cardalis™ to benazepril alone in client-owned dogs when dosed with concurrent therapy to manage congestive heart failure. The dogs had radiographic evidence of congestive heart failure and clinical signs associated with left-sided AVVI. Both females and males (spayed/neutered and intact) were enrolled in the study, with a wide range of ages and weights. Most were older, small-breed dogs. All dogs received concurrent oral furosemide during the study, dosed according to the severity of the disease (up to 8 mg/kg/day), to manage pulmonary edema. Injectable furosemide was allowed only if it was used in place of an equivalent oral dose. Digoxin and calcium channel blockers were allowed to control supraventricular arrhythmias. Compared to the benazepril-only group, the Cardalis™ group had a lower treatment failure rate on Day 360 and a longer median time-to-failure.

Overall, the adverse reactions were similar in both groups and included anorexia, vomiting, lethargy, diarrhea, renal insufficiency, collapse, hepatopathy, and urinary incontinence. Renal insufficiency was seen more frequently in dogs treated with Cardalis™; however, renal function values were not statistically different between the treatment groups. While the renal insufficiency may be related to the administration of Cardalis™, this finding may also be related to the administration of furosemide, a potent diuretic-saluretic that is known to cause dehydration and electrolyte imbalances. The administration of furosemide along with Cardalis™ made it difficult to determine the cause of the renal insufficiency.

Because all dogs in the study had congestive heart failure, there was a high fatality rate, but the incidence of death, including euthanasia and sudden death, was similar in both groups. In most cases, death was due to the progression of heart disease or the clinical signs associated with congestive heart failure. Deaths of unknown cause were presumed to be cardiac in nature. Serum magnesium and potassium levels were significantly higher in the Cardalis™ group, although the mean levels were within the reference ranges and didn't change significantly over time. These electrolyte changes are consistent with the potassium-sparing properties of spironolactone.

The sponsor also conducted a 6-month safety study in young, healthy, male and female Beagle dogs. The dogs were dosed at 0X, 1X, 3X, or 5X the maximum dose exposure of

Cardalis™ daily for 6 months. The 1X dose used in the safety study was twice the labeled dose of 2 mg/kg spironolactone and 0.25 mg/kg benazepril hydrochloride. Because small breed dogs often develop congestive heart failure due to AVVI, the 1X dose was based on the maximum possible exposure for a small dog based on tablet size. When dosed with the smallest tablet, some small dogs could receive up to 4 mg/kg spironolactone and 0.5 mg/kg benazepril hydrochloride (the 1X dose used in the safety study).

The drug was well-tolerated in all treatment groups. Treated dogs had increased mean serum potassium and aldosterone levels, due to the potassium-sparing nature of spironolactone and antagonism of aldosterone receptors, respectively. Treated dogs also had decreased mean plasma ACE activity, consistent with the ACE inhibitory action of benazepril hydrochloride. Microscopic changes were seen in the zona glomerulosa region of the adrenal glands of both males and females and the prostate glands of males, consistent with the physiologic action of spironolactone in these organs.

**Conclusions**

Based on the data submitted by the sponsor for the approval of Cardalis™, FDA determined that the drug is safe and effective when used according to the label.

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## **I. GENERAL INFORMATION**

### **A. File Number**

NADA 141-538

### **B. Sponsor**

Ceva Sante Animale,  
10 Avenue de la Ballastière,  
33500 Libourne, France

Drug Labeler Code: 013744

U.S. Agent Name and Address:

Alicia Henk  
Ceva Animal Health  
8735 Rosehill Rd  
Lenexa, KS 66215

### **C. Proprietary Name**

Cardalis™

### **D. Drug Product Established Name**

Spironolactone and benazepril hydrochloride chewable tablets

### **E. Pharmacological Category**

Aldosterone antagonist (spironolactone)  
Angiotensin-converting enzyme (ACE) inhibitor (benazepril hydrochloride)

### **F. Dosage Form**

Chewable Tablet

### **G. Amount of Active Ingredient**

20 mg spironolactone and 2.5 mg benazepril hydrochloride  
40 mg spironolactone and 5 mg benazepril hydrochloride  
80 mg spironolactone and 10 mg benazepril hydrochloride

### **H. How Supplied**

Cardalis™ chewable tablets for dogs are available in 3 sizes of flavored, half-scored oblong tablets: 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. Each size is available in 30-count bottles.

### **I. Dispensing Status**

Prescription (Rx)

## **J. Dosage Regimen**

Cardalis™ administration should begin after pulmonary edema is stabilized. Cardalis™ should be administered orally once daily at a dose of 0.9 mg/lb (2 mg/kg) spironolactone and 0.11 mg/lb (0.25 mg/kg) benazepril hydrochloride, according to the dog's body weight, using a suitable combination of whole and/or half tablets. All tablet strengths are scored and the calculated dosage according to the dog's weight should be to the nearest half-tablet increment. Cardalis™ should be administered with food.

## **K. Route of Administration**

Oral

## **L. Species/Class**

Dogs

## **M. Indication**

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

# **II. EFFECTIVENESS**

## **A. Dosage Characterization**

### **1. Dose Selection**

Doses of 0.9 mg/lb (2 mg/kg) for spironolactone and 0.11 mg/lb (0.25 mg/kg) for benazepril hydrochloride administered orally with food once daily were selected based on the results of the following studies.

- a. Spironolactone: The dose for spironolactone was based on 1) a pharmacokinetic extrapolation of the dose from humans to dogs, 2) a dose titration study using an experimental model of hyperaldosteronism in dogs, and 3) a field study assessing the effectiveness of spironolactone for the management of congestive heart failure in dogs.

Data from human studies demonstrated that doses of spironolactone ranging from 12.5 mg to 75 mg effectively block aldosterone receptors in patients with congestive heart failure. Using an allometric approach that established the relationship between body weight and drug clearance, the pharmacokinetic extrapolation from clinical data obtained in humans predicted a dose between 1.7 mg/kg and 2.6 mg/kg in dogs would be the most effective.

A model of hyperaldosteronism in dogs was used to establish a relationship between the dose and the effect of spironolactone on the urinary sodium:potassium ratio. Hyperaldosteronism was induced by administration of aldosterone intramuscularly resulting in a decrease in the urinary sodium:potassium ratio. Spironolactone was administered

orally with food at a single dose of 0.75 mg/kg, 2 mg/kg, or 8 mg/kg. Spironolactone reversed the effect of aldosterone on the urinary sodium:potassium ratio in a dose-dependent manner reaching maximal effect at doses  $\geq 2$  mg/kg. The inhibitory effect of doses  $\geq 2$  mg/kg lasted over 12 hours with measurable levels of active metabolite in plasma after 24 hours. A dosing interval of once daily was proposed based on integration of the pharmacokinetics of spironolactone with pharmacodynamic data.

Data collected from European field studies further supported the dose selection of 2 mg/kg once daily. Field studies evaluating spironolactone at a dose of 2 mg/kg administered orally once daily in combination with standard therapy (ACE inhibitors, furosemide, and digoxin, if needed) showed a lower mortality rate (death or euthanasia related to congestive heart failure) in dogs with cardiac disease.

- b. Benazepril hydrochloride: The dose for benazepril hydrochloride was based on 1) a dose titration study and 2) a field study in dogs with congestive heart failure.

A dose titration study assessed the effect of benazepril hydrochloride on the inhibition of ACE activity in the plasma of dogs after oral administration at the following doses: 0.125, 0.25, 0.5, or 1.0 mg/kg. All doses of benazepril hydrochloride inhibited plasma ACE activity. The 0.25 mg/kg dose was the lowest dose that caused maximal ACE inhibition after a single dose and at steady state. After 24 hours, the ACE inhibition was still high, thereby supporting once daily dosing. Increasing the dose above 0.25 mg/kg did not have a greater effect on plasma ACE activity.<sup>1</sup>

In a European field study in dogs with naturally occurring congestive heart failure, benazepril hydrochloride was administered at a minimum dose of 0.25 mg/kg once daily and compared to a placebo. Additional cardiac therapies were permitted. The mean survival time, defined as the time of death or withdrawal due to heart failure, was 2.7 times longer with benazepril compared to standard therapy alone (428 versus 158, respectively).<sup>2</sup>

2. Combination of benazepril and spironolactone: A pharmacokinetic and pharmacodynamic study was conducted in dogs using commercially available spironolactone and benazepril hydrochloride to determine if either active ingredient altered the pharmacokinetics or pharmacodynamics of the other. The pharmacodynamic outcomes were the urinary sodium:potassium ratio for spironolactone and plasma ACE activity for benazepril hydrochloride. The presence of benazepril hydrochloride did not alter the pharmacokinetics of 7a-

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<sup>1</sup> King J.N., Mauron C., Kaiser G. Pharmacokinetics of the active metabolite of benazepril, benazeprilat, and inhibition of plasma angiotensin-converting enzyme activity after single and repeated administrations to dogs. *Am J Vet Res* 1995, 56, 1620-1628.

<sup>2</sup> The BENCH Study Group. The effect of benazepril on survival times and clinical signs of dogs with congestive heart failure: Results of a multicenter, prospective, randomized double blinded, placebo-controlled, long-term clinical trial. *J Vet Cardiology* 1999, 1, 7-18.

thiomethyl-spirolactone or canrenone, the active metabolites of spironolactone. The presence of benazepril hydrochloride did not alter the pharmacodynamics of spironolactone. However, the presence of spironolactone increased the oral bioavailability of benazeprilat, the active metabolite of benazepril hydrochloride. The presence of spironolactone did not alter the pharmacodynamics of benazepril hydrochloride.

Spirolactone is mainly used for its antifibrotic effects via its aldosterone blocking action<sup>3</sup>, but the underlying mechanism by which mineralocorticoid receptor antagonists reduce the incidence of sudden cardiac death in congestive heart failure has not been fully elucidated.<sup>4</sup> The apparently synergistic effect of spironolactone added to an ACE inhibitor is likely exerted through control of aldosterone escape or aldosterone breakthrough (ABT). ABT is a condition where ACE inhibitors alone fail to suppress the renin angiotensin aldosterone system (RAAS), and occurs through both an upstream accumulation of renin and through alternative pathways of aldosterone generation not dependent on the RAAS when ACE inhibitor therapy is instituted.<sup>5</sup> Because spironolactone addresses only the downstream, aldosterone-mediated activity of the RAAS, is a downstream inhibitor, and can be incomplete in its activity, it is not effective as a single-agent therapy to manage the clinical signs of congestive heart failure in dogs due to AVVI.

## **B. Substantial Evidence**

### **1. 12-month Field Safety and Effectiveness Study**

**Title:** Evaluation Of Cardalis™, In Comparison To Benazepril, In Dogs With Heart Failure Caused By Left Atrioventricular Valvular Insufficiency (AVVI). (Study No. US/CLI/C635/1101)

**Study Dates:** February 22, 2012 to December 07, 2019

**Study Locations:** This multi-center study was conducted at 27 clinical sites throughout the United States. The study investigators were veterinary cardiologists or internists with extensive training in cardiology and were all board-certified by the American College of Veterinary Internal Medicine (ACVIM).

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<sup>3</sup> Madron, E., King J. N., Strehlau, G., & White, R.V. (2011). Survival and echocardiographic data in dogs with congestive heart failure caused by mitral valve disease and treated by multiple drugs: a retrospective study of 21 cases. *Can Vet J*, 52(11): 1219-25.

<sup>4</sup> Esposito, C. T., Varahan, S., Jeyaraj, D., Lu, Y. & Stambler, B. S. (2013). Spironolactone Improves the Arrhythmogenic Substrate in Heart Failure by Preventing Ventricular Electrical Activation Delays Associated with Myocardial Interstitial Fibrosis and Inflammation. *J Cardiovasc Electrophysiol*, 24: 806-812.

<sup>5</sup> Hargovan M, Ferro A (2014). Aldosterone synthase inhibitors in hypertension; current status and future possibilities. *JRSM Cardiovasc Dis*. 0(0):1-9.



Leesburg, VA	Englewood, CO	Coral Springs, FL
Richmond, VA	Manakin-Sabot, VA	Blacksburg, VA
Pittsburgh, PA	Overland Park, KS	Kirkland, WA
Portland, OR	Houston, TX	New York, NY
West Palm Beach, FL	Rohnert Park, CA	Boulder, CO
Worthington, OH	Los Angeles, CA	Cincinnati, OH
Tinton Falls, NJ	San Francisco, CA	Chicago, IL
Raleigh, NC	San Diego, CA	Orange Park, FL
San Leandro, CA	Columbia, SC	Sacramento, CA

**Study Design:** This study was conducted in accordance with Good Clinical Practices (GCP) guidelines.

**Objectives:** To evaluate the safety and effectiveness of Cardalis™ compared to the active control, benazepril hydrochloride, for the management of clinical signs of congestive heart failure in dogs due to AVVI under field conditions, and to demonstrate the contribution of spironolactone to the effectiveness of the Cardalis™ combination drug product.

**Study Animals:** A total of 569 client-owned dogs (274 females and 295 males, spayed/neutered or intact) were enrolled in the study, ranging in age from 3 to 19 years old, and weighing between 5.0 and 155 lb (2.3 to 70.5 kg). Most were older, small-breed dogs with a mean age of 11.0 years and a mean body weight of 19.9 lb (9.0 kg). The most common breeds were mixed breed (25%), Cavalier King Charles Spaniel (9.8%), Chihuahua (9.7%), Shih Tzu (5.4%), Maltese (5.4%), Dachshund (5.1%), and Yorkshire Terrier (4.0%).

Enrolled dogs demonstrated radiographic evidence of congestive heart failure prior to enrollment or on Day 0 and exhibited clinical signs associated with left-sided AVVI, including exercise intolerance and/or dyspnea, echocardiographic evidence of left-atrial enlargement, moderate-to-severe mitral regurgitation, and presence of a left-sided cardiac murmur. Dogs were excluded from the study if they had one of the following: acquired heart disease other than left-sided AVVI, a congenital heart defect, current positive heartworm antigen test, or syncope not related to heart disease, and dogs intended for breeding or known to be pregnant or lactating.

**Experimental Design:** This was a well-controlled, multi-center, masked, randomized, field study in client-owned dogs. The study included two treatment groups. The investigational product, Cardalis™, was compared to benazepril hydrochloride alone (active control) using a superiority analysis. The primary effectiveness outcome was percent treatment failure on Day 360.

**Table II.1: Treatment Groups**

<b>Treatment Group</b>	<b>Dose</b>	<b>Safety Population</b>	<b>Effectiveness Population</b>
Cardalis™	2 mg/kg spironolactone and 0.25 mg/kg benazepril HCl	284	216
Control	0.25 mg/kg benazepril HCl	285	198

**Drug Administration:** Of the 569 dogs enrolled in the study, 284 were treated with Cardalis™ chewable tablets at a dose of 2 mg/kg spironolactone and 0.25 mg/kg benazepril hydrochloride once daily by mouth and 285 were treated with benazepril hydrochloride alone in the same chewable tablet formulation at a dose of 0.25 mg/kg once daily by mouth. Doses were administered with food or within 30 minutes of feeding.

All dogs received concomitant oral furosemide during the study, dosed according to the severity of disease (up to 8 mg/kg/day), to manage pulmonary edema. The use of injectable furosemide was permitted during the study evaluation period only if used in place of an equivalent oral dose. Digoxin and calcium channel blockers were allowed during the study evaluation period for control of supraventricular arrhythmias. All non-cardiac medications that did not interfere with the evaluation of the study endpoints were allowed.

**Measurements and Observations:** Baseline physical examination, assessment of the clinical signs of cardiac failure, Functional Evaluation of Cardiac Health (FETCH) quality of life questionnaire,<sup>6</sup> thoracic radiographs, systemic arterial blood pressure, electrocardiogram, echocardiogram, hematology, serum chemistry, urinalysis, heartworm antigen, heart murmur intensity, ISACHC (International Small Animal Cardiac Health Council) heart disease classification, and serum N-terminal pro-brain natriuretic peptide (NTproBNP) were performed prior to initiating treatment.

The dogs were reevaluated on Day 7 ( $\pm 2$ ), Day 30 ( $\pm 4$ ), Day 90 ( $\pm 7$ ), Day 270 ( $\pm 7$ ), and Day 360 ( $\pm 7$ ). Physical examination, FETCH questionnaire, thoracic radiographs, systemic arterial blood pressure, and serum chemistry were performed at all visits. Hematology, electrocardiogram, echocardiogram, urinalysis, and serum NTproBNP were repeated at various intervals.

Safety was monitored throughout the study through the documentation of clinical history between visits, repeat physical and cardiac examinations, the monitoring of clinical pathology parameters, and documentation of adverse events. Study personnel and owners responsible for all evaluations were masked to treatment assignment for the entirety of the study.

The palatability of Cardalis™ was assessed by the owner for the first 14 days of the study. The dog was offered Cardalis™ by hand or in an empty bowl. If Cardalis™ was not accepted within 5 minutes, it was then offered with or on top of food. If not fully consumed within 5 minutes the owner was advised to pill the dog.

**Statistical Methods:** The rate of treatment failure (percent treatment failure on Day 360) was the primary effectiveness variable used to compare Cardalis™ to the active control, benazepril hydrochloride alone. The primary variable was binary treatment outcome (success or failure) on Day 360 ( $\pm 7$

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<sup>6</sup> Freeman LM, Rush JE, Farabaugh AE, Must A. Development and evaluation of a questionnaire for assessing health-related quality of life in dogs with cardiac disease. *Journal of the American Veterinary Medical Association*. 2005; 226(11):1864-1868.

days). The percent of treatment failure and 95% confidence intervals were evaluated with a generalized linear mixed model. The model included treatment as a fixed effect, and site and site-by-treatment interaction as random effects. The significance level was 0.05 (two-sided).

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.

Secondary treatment outcomes included treatment failure at Days 30, 90, 180, 270, and 360; progression of the individual signs of cardiac failure; and progression of quality of life scoring (defined by sum of FETCH scores). Secondary treatment outcomes were evaluated using the same model as the primary outcome, by visit time, at a significance level of 0.05 (two-sided).

**Results:** Primary Effectiveness Analysis: The primary effectiveness evaluation included a total of 414 dogs, with 216 receiving Cardalis™ and 198 receiving benazepril hydrochloride alone. Dogs were excluded from the analysis of effectiveness for the following reasons: treatment failure on or before Day 7 (non-stabilization), improper dosing (by greater than 20%), administration of injectable furosemide in addition to the oral dose, morbidity or mortality due to non-cardiac disease or illness, failure of sites to attain minimum enrollment, and owner non-compliance with study procedures.

Of the 414 dogs included in the effectiveness evaluation, 48 of the 216 dogs treated with Cardalis™ and 27 of the 198 dogs treated with benazepril hydrochloride alone successfully completed the study through Day 360. The rate of failure in the Cardalis™ treatment group estimated from the model analysis was statistically different (P = 0.0433) and numerically lower than that of the benazepril control group. The primary effectiveness results are summarized in Table II.2.

**Table II.2: Treatment Failure Rates by Treatment Group (Least Square Means) on Day 360**

Group	N	Percent of Treatment Failures <sup>a,b</sup>	95% Confidence Interval	P-value <sup>c</sup>
Cardalis™	216	80.59%	72.57, 86.69%	0.0433
Benazepril HCl	198	88.09%	81.40, 92.59%	-

<sup>a</sup> Back-transformed from the logit transformation used in the statistical analysis, which included random effects associated with study site and the site by treatment interaction.

<sup>b</sup> Calculated based on individual animal results.

<sup>c</sup> P-value when comparing treatment and control groups.

Time to Treatment Failure: At each time point evaluated, the percentage of treatment failures in the Cardalis™ group was lower than in the group treated with benazepril hydrochloride alone, and this difference was statistically significant at each evaluation after the Day 30 visit. A summary of treatment failure rates at each evaluation point is provided in Table II.3. The dogs in the

Cardalis™ group exhibited a longer median time-to-failure when compared to the benazepril hydrochloride alone group.

**Table II.3: Summary of Treatment Failure Rate by Visit (Least Square Means)**

Day	Group	Percent of Treatment Failures <sup>a</sup>	95% Confidence Interval	P-value <sup>b</sup>
30	Cardalis™	20.0%	14.3, 27.2	0.4621
30	Benazepril HCl	23.2%	16.8, 31.1	-
90	Cardalis™	47.7%	39.3, 56.3	0.0335
90	Benazepril HCl	59.5%	50.6, 67.8	-
180	Cardalis™	68.1%	59.5, 75.6	0.0378
180	Benazepril HCl	78.2%	70.2, 84.5	-
270	Cardalis™	73.0%	64.6, 80.1	0.0132
270	Benazepril HCl	84.4%	77.1, 89.7	-
360	Cardalis™	78.1%	67.7, 84.6	0.0423
360	Benazepril HCl	86.4%	79.3, 91.3	-

<sup>a</sup> Calculated based on individual animal results.

<sup>b</sup> P-value when comparing treatment and control groups.

**Palatability:** Of the 233 dogs that were offered Cardalis™ once daily for 14 days, it was voluntarily accepted in 87.6% of the 3178 reported doses; 40.75% of those dogs accepted Cardalis™ without food and 46.82% with food.

**Concomitant Medications:** In addition to the diuretic furosemide administered to all dogs enrolled in the study, dogs also received a variety of concomitant medications during the study, including: digoxin, calcium channel blockers, antiparasitics, analgesics/anti-inflammatories, antibacterials, routine canine vaccines, respiratory treatments, and gastrointestinal treatments.

**Adverse Reactions:** Field safety was assessed in 569 dogs with 284 in the Cardalis™ group and 285 in the active control group receiving the same chewable tablet formulation containing only benazepril hydrochloride. Table II.4 summarizes the adverse reactions not directly related to the progression of disease that occurred in greater than 5% of dogs treated with Cardalis™. Adverse events observed during the study that were considered directly related to the progression of disease included coughing, exercise intolerance, pulmonary edema, and cardiac insufficiency.

**Table II.4: Adverse Reactions Occurring in  $\geq 5\%$  of Cardalis™-Treated Dogs**

<b>Adverse Reaction</b>	<b>Cardalis™ N=284 (%)</b>	<b>Benazepril HCl N=285 (%)</b>
Anorexia	107 (38%)	113 (40%)
Vomiting	70 (25%)	51 (18%)
Lethargy	44 (16%)	41 (14%)
Diarrhea	43 (15%)	41 (14%)
Renal Insufficiency	31 (11%)	19 (6.7%)
Collapse	16 (5.6%)	12 (4.2%)
Hepatopathy	16 (5.6%)	8 (2.8%)
Urinary Incontinence	15 (5.3%)	27 (9.5%)

The following adverse reactions were reported in fewer than 5% of the study animals, in decreasing order: urine abnormalities, fluid in abdomen, ataxia, weight loss, digestive 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 furosemide. 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 presumed to be cardiac in nature.

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 treated with Cardalis™ was removed from the study at Day 7 because it developed hyperkalemia.

**Conclusion:** Cardalis™ is safe and effective when used with concurrent therapy (e.g., furosemide, etc.) for the management of clinical signs of mild, moderate or severe congestive heart failure in dogs due to left-sided AVVI.

### **III. TARGET ANIMAL SAFETY**

#### **A. Margin of Safety Study**

**Title:** Six-Month (26 Week) Target Animal Safety Study Of Cardalis™ For Oral Administration In Dogs. (Study No. ST-TOL/C635.1/0946)

**Study Dates:** December 2, 2009 to June 23, 2010

**Study Location:** Auxvasse, MO

**Study Design:** This study was conducted in accordance with Good Laboratory Practices (GLP) regulations.

**Objective:** To assess the toxicity of Cardalis™ in dogs when orally dosed daily at 1X, 3X, and 5X the maximum exposure dose (4 mg/kg spironolactone and 0.5 mg/kg benazepril hydrochloride) for a period of six months (26 weeks).

**Study Animals:** 32 healthy Beagle dogs (16 male and 16 female), non-pregnant, non-lactating, approximately 1 year of age and weighing between 9.7 and 14.1 kg at the beginning of the treatment period, were randomly allocated to four treatment groups (0X, 1X, 3X, 5X). The 1X dose used in the safety study was twice the labeled dose of 2 mg/kg spironolactone and 0.25 mg/kg benazepril hydrochloride. Because small breed dogs often develop congestive heart failure due to AVVI, the 1X dose was based on the maximum possible exposure for a small dog based on tablet size.

**Table III.1: Treatment Groups**

<b>Group</b>	<b>Daily Dose (mg/kg)</b>	<b>Number and Gender of Animals</b>
Untreated	0 spironolactone and 0 benazepril HCL	8 (4 male, 4 female)
1X	4 spironolactone and 0.5 benazepril HCL	8 (4 male, 4 female)
3X	12 spironolactone and 1.5 benazepril HCL	8 (4 male, 4 female)
5X	20 spironolactone and 2.5 benazepril HCL	8 (4 male, 4 female)

**Drug Administration:** The Cardalis™ test article was supplied as scored tablets containing spironolactone and benazepril hydrochloride in a fixed ratio in three tablet strengths to accommodate differences in body weight. Throughout the study, dogs were administered the appropriate level of test article once a day orally, with food, for 26 weeks.

**Measurements and Observations:** Daily measurements were made for clinical observations (i.e., appearance, behavior, attitude) and quantitative food consumption. Throughout the study, physical examinations, body weights, qualitative food and water consumption, electrocardiogram, blood pressure, hematology, serum chemistry, coagulation profiles, and urinalysis were performed or measured. In addition, plasma ACE activity, aldosterone, testosterone, progesterone, and cortisol levels were measured. Blood samples were collected on Days 7, 90, and 181 to measure plasma concentrations of metabolites: canrenone and 7 $\alpha$ -thiomethyl-spirolactone (active metabolites of spironolactone), and benazeprilat (active metabolite of benazepril hydrochloride). Gross pathology, organ weights, and histopathology were performed on all dogs at the end of the study.

**Statistical Methods:** The unit of observation and statistical analysis was the individual dog. For continuous outcomes measured only once during the study, ANOVA (the MIXED procedure in SAS, SAS Institute, Cary, North Carolina) was used to evaluate a model containing treatment, sex, and sex-by-treatment

interaction as fixed effects. Continuous variables measured at multiple times during the study were analyzed by a repeated measures analysis of covariance, with treatment, sex, day, treatment by sex, sex-by-day, treatment-by-day, and treatment-by-sex-by-day as fixed effects, and animal identified as the subject in the repeated statement (the MIXED procedure in SAS, RMANCOVA). For categorical variables, outcomes deemed clinically relevant, and where sufficient data were available, Fisher's exact test was used to evaluate the treated groups vs. control in a pair-wise fashion. All tests were conducted at the 0.10 level of significance.

**Results:** There were no treatment-related abnormal individual animal findings noted in the daily clinical observations or physical examination.

There were no statistically significant differences between the groups administered Cardalis™ and the control group for qualitative food consumption. For female animals, quantitative water intake for the 3X group was slightly lower than that for the controls (0X group). For males, the 3 groups administered Cardalis™ (1X, 3X, and 5X) had substantially increased water intake over the course of the study compared with their corresponding controls (0X). All animals maintained their body weight for the duration of the study, and there were no apparent trends in body weight with respect to dose groups or study day.

There was a general pattern of decreased red cell mass (mean red blood cell count, hematocrit, and hemoglobin) in the groups administered Cardalis™ compared to the control group, particularly for the highest dose (5X) group, but these parameters remained within the reference range. Mean serum potassium levels were increased in the 3 groups administered Cardalis™ (1X, 3X and 5X) compared with the control group (0X) at all time points, but potassium levels remained within the reference range.

There were no abnormal electrocardiographic or blood pressure findings in any treatment group. The dogs in the 5X group had lower mean heart rates compared to the other groups at the end of the study.

Mean plasma ACE activity was lower in dogs administered Cardalis™ compared to the control group. Mean serum aldosterone levels were increased in a dose-dependent manner in dogs receiving Cardalis™. There were no test-article-related changes in testosterone, progesterone, and cortisol levels between groups.

On necropsy, there were no macroscopic findings related to the administration of Cardalis™. Sporadic macroscopic observations involving the lungs, kidneys, and small intestine were reported. There were statistically significant differences in organ weights seen in the brain, lungs, and prostate. The changes in the brain and lungs were not considered clinically significant or treatment related. Prostate weights (absolute, per body) decreased in the groups administered Cardalis™ (1X, 3X and 5X) compared to the control group (0X), and these were statistically significant in the 3X and 5X groups.

Microscopic observations related to administration of Cardalis™ included mild to moderate thickening of the zona glomerulosa of the adrenal glands of males and females in the 3X and 5X dose groups. The incidence of this finding was dose-

dependent, but the severity was not. Dose-dependent atrophy of the glandular epithelium of the prostate gland of slight to marked intensity was noted in male dogs in the 3X and 5X groups. Findings in other organs and tissues were not considered drug related.

Systemic exposure to canrenone, 7 $\alpha$ -thiomethyl-spirolactone, and benazeprilat was shown at the three dose levels throughout the study, with no apparent gender effect. For canrenone steady-state was achieved by Day 90 and accumulation was approximately 30%. Canrenone systemic exposure was more than dose proportional over the dose range of 4 to 20 mg/kg of spironolactone. Systemic exposure to 7 $\alpha$ -thiomethyl-spirolactone was variable by study day and dose of spironolactone. Steady state was achieved by Day 90 in the 1X and 5X dose groups. In the 3X dose group steady state was not achieved by the end of the study. In the 1X group 7 $\alpha$ -thiomethyl-spirolactone accumulation was 30% by Day 90 and 15% by Day 181. In the 5X group there was no accumulation. For Days 7, 90, and 181, systemic exposure was proportional to dose. Benazeprilat systemic exposure was more than dose proportional over the dose range 0.5 to 2.5 mg/kg of benazepril, steady state was achieved by Day 90, and there was no accumulation.

**Conclusion:** The oral administration of Cardalis™ (spironolactone and benazepril hydrochloride chewable tablets) at doses up to 5X the maximum labeled dose for 6 months was well-tolerated in healthy dogs. The increase in mean serum potassium and aldosterone levels, decrease in mean plasma ACE activity, and changes in the prostate and the adrenal glands are consistent with the aldosterone receptor antagonism of spironolactone.

#### **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 Cardalis™:

Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of ingestion by humans.

#### **VI. AGENCY CONCLUSIONS**

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that Cardalis™, when used according to the label, is safe and effective for use with concurrent therapy (e.g. furosemide, etc.) for the management of clinical signs of mild, moderate, or severe congestive heart failure in dogs due to atrioventricular valvular insufficiency (AVVI).



**A. Marketing Status**

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is needed for diagnosis of congestive heart failure in dogs due to AVVI, the selection of appropriate concurrent therapy, monitoring the safe use of the product, and treatment of any adverse reactions.

**B. Exclusivity**

Cardalis™, as approved in our approval letter, qualifies for FIVE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the FD&C Act because this is the first time we are approving the active ingredients in a new animal drug application submitted under section 512(b)(1) of the FD&C Act.

**C. Patent Information**

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