

Frequently asked questions

At what stage of heart failure should Cardalis® be used?

Cardalis® should be given as part of your standard heart failure therapy as soon as clinical signs (such as exercise intolerance, coughing and/or dyspnoea) appear*.

Can Cardalis® be used alongside pimobendan?

Yes, it has been shown that Cardalis® is well tolerated when combined with pimobendan¹²

Do I need to reduce the furosemide dose when using Cardalis®?

No, the dose of furosemide that you need to control oedema will usually remain the same. The diuretic effect of spironolactone is very mild and the main reason for using Cardalis® is to counteract the harmful effects of angiotensin II and aldosterone, which include vasoconstriction and cardiovascular re-modelling/fibrosis^{2,3}.



To find out more about how you can upgrade your heart failure patients* to Cardalis®, visit www.ceva.co.uk or contact the practice support team on **(01494) 781510**



To learn about the management of heart failure in practice from leading experts, visit the following free CPD website - www.cardioacademy.cevalearn.com



Why not also try the Cardalis® iPhone App, available free from iTunes, which allows owners to measure respiratory rate at home and also provides a medication reminder service

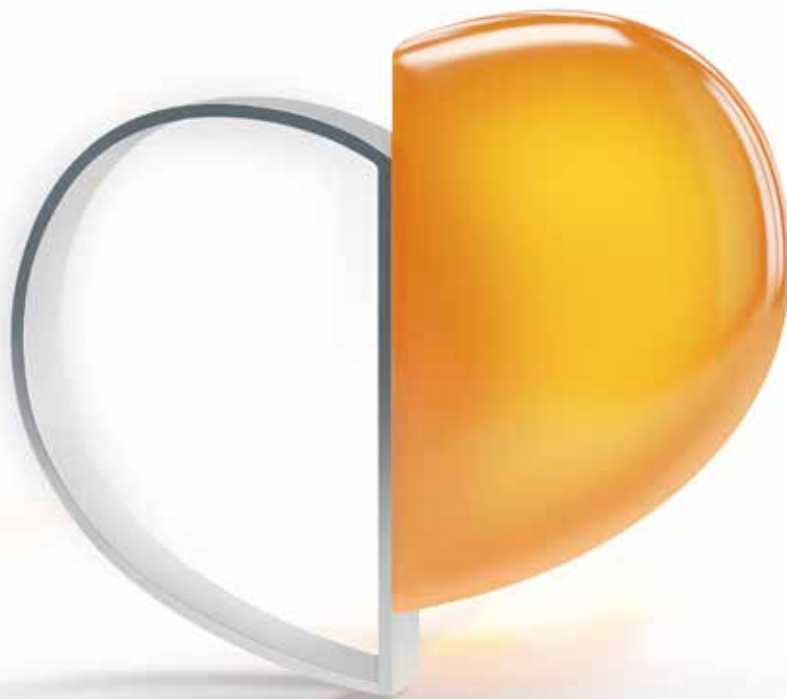


* For the home-care treatment of congestive heart failure caused by chronic degenerative valvular disease in dogs (with diuretic support as appropriate)

References: 1. Oyama, M.A. (2009), Neurohormonal activation in canine degenerative mitral valve disease: implications on pathophysiology and treatment, *Journal of Small Animal Practice*, 50 (Suppl/1), 3-11. 2. Atkins, C.E., Häggström, J. (2012), Pharmacological management of myxomatous mitral valve disease in dogs, *Journal of Veterinary Cardiology*, 14, 165-184. 3. Ovaert, P. et al. (2010), Aldosterone receptor antagonists – how cardiovascular actions may explain their beneficial effects in heart failure, *Journal of Veterinary Pharmacology and Therapeutics*, 33(2), 109-117. 4. Sayer, M.B. et al. (2009), Acute effect of pimobendan and furosemide on the circulating renin-angiotensin-aldosterone system in healthy dogs, *Journal of Veterinary Internal Medicine*, 23, 1003 – 1006. 5. Lantis, A.C. (2009), The effect of furosemide and pimobendan on the renin-angiotensin-aldosterone system (RAAS) in dogs, *ACVIM Forum Abstracts*, 685. 6. Häggström, J. et al. (1996), Effects of long-term treatment with enalapril or hydralazine on the renin-angiotensin-aldosterone system and fluid balance in dogs with naturally acquired mitral valve regurgitation, *American Journal of Veterinary Research*, 57 (11), 1645 – 1652. 7. Lantis A.C. et al. (2010), Aldosterone Escape in Furosemide-Activated Circulating Renin-Angiotensin-Aldosterone System (RAAS) in Normal Dogs, *ACVIM Congress Proceedings*. 8. Bernay, F. et al. (2010), Efficacy of Spironolactone on Survival in Dogs with Naturally-occurring Mitral Regurgitation caused by Myxomatous Mitral Valve Disease, *Journal of Veterinary Internal Medicine*, 24(2), 331-341. 9. Bench study group (1999), 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, *Journal of Veterinary Cardiology*, 1(1), 7-19. 10. Cardalis® SPC. 11. Ollivier, E., Grassi, V. (2012), Concomitant use of the FETCH questionnaire and the veterinary evaluation to assess quality of life of cardiac dogs treated with a veterinary product combining spironolactone and benazepril (Cardalis®) in healthy and cardiac dogs, *ECVIM Congress Proceedings and Poster*. 12. Ollivier, E. et al. (2012), Safety of a veterinary product combining spironolactone and benazepril (Cardalis®) in healthy and cardiac dogs, *ECVIM Congress Proceedings and Poster*. 13. Coussanes, E. et al. (2012), Six month target animal safety of spironolactone and benazepril hydrochloride combination (Cardalis®) for oral administration in dogs, *EAVIP Congress Abstract*, 8-12th July. 14. Martin, M. (2012), Canine Congestive Heart Failure: An Approach To Case Management, *Veterinary Times*, 23rd January. 15. Atkins, C. (2011), Finding a consensus on canine CVHD, *NAVC Clinicians Brief*, July.

Cardalis® contains 2.5mg benazepril/20mg spironolactone, 5mg benazepril/40mg spironolactone and 10mg benazepril/80mg spironolactone. **Uses:** For the treatment of congestive heart failure caused by chronic degenerative valvular disease in dogs (with diuretic support as appropriate). **Dosage and Administration:** For oral administration. Once daily at a dose of 0.25mg/kg bodyweight benazepril and 2mg/kg spironolactone. The tablets should be administered with food. The fixed combination product should only be used in dogs which require both active substances to be administered concomitantly at this fixed dose. **Contraindications, warnings etc:** Do not use during pregnancy and lactation. Do not use in dogs intended or used for breeding. Do not use in dogs suffering from hypoadrenocorticism, hyperkalaemia or hyponatraemia. Do not administer in conjunction with Non Steroidal Anti-Inflammatory Drugs (NSAIDs) to dogs with renal insufficiency. Do not use in case of hypersensitivity to Angiotensin-Converting Enzyme inhibitors (ACE inhibitors) or to any of the excipients. Do not use in cases of cardiac output failure due to aortic or pulmonary stenosis. **Special precautions for use:** Kidney function and serum potassium levels should be evaluated before initiating the treatment with benazepril and spironolactone, especially in dogs which may suffer hypoadrenocorticism, hyperkalaemia or hyponatraemia. Unlike in humans, an increased incidence of hyperkalaemia was not observed in clinical trials performed in dogs with this combination. However, regular monitoring of renal function and serum potassium levels is recommended in dogs with renal impairment, as they may have an increased risk of hyperkalaemia during treatment with this product. Due to the antiandrogenic effect of spironolactone, it is not recommended to administer the veterinary medicinal product to growing dogs. To be used with caution to treat dogs with hepatic dysfunction because it may alter the extensive biotransformation of spironolactone in liver. **Operator warning:** Wash hands after use. People with known hypersensitivity to benazepril or spironolactone should avoid contact with the veterinary medicinal product. Pregnant women should take special care to avoid accidental oral exposure because ACE inhibitors have been found to affect the unborn child during pregnancy in humans. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. **Adverse reactions:** A reversible prostatic atrophy is often observed in entire male dogs treated with spironolactone. **Use during pregnancy, lactation or lay:** Do not use during pregnancy and lactation. Embryotoxic effects (foetal urinary tract malformation) were seen in trials of benazepril with laboratory animals (rats) at maternally non-toxic doses. **Interaction with other medicinal products and other forms of interaction:** Furosemide has been used together with this combination of benazepril hydrochloride and spironolactone in dogs with heart failure without any clinical evidence of adverse interactions. The concomitant administration of this veterinary medicinal product with other anti-hypertensive agents (e.g. calcium channel blockers, β-blockers or diuretics), anaesthetics or sedatives may potentially lead to additive hypotensive effects. The concomitant administration of this veterinary medicinal product with other potassium-sparing treatments (such as β-blockers, calcium channel blockers, angiotensin receptor blockers) may potentially lead to hyperkalaemia. The concomitant use of NSAIDs with this veterinary medicinal product may reduce its anti-hypertensive effect, its natriuretic effect and increase the level of serum potassium. Therefore, dogs treated concomitantly with an NSAID should be closely monitored and correctly hydrated. The administration of deoxytocosterone with the product may lead to a moderate reduction of the natriuretic effects (reduction of urinary sodium excretion) of spironolactone. Spironolactone decreases digoxin elimination and hence raises digoxin plasma concentration. As the therapeutic index for digoxin is very narrow, it is advisable to monitor closely dogs receiving both digoxin and a combination of benazepril hydrochloride and spironolactone. Spironolactone may cause both induction and inhibition of cytochrome P450 enzymes and could affect the metabolism of other substances utilizing these metabolic pathways. Therefore, the product should be used with caution with other veterinary medicinal products which induce, inhibit, or which are metabolised by these enzymes. **Overdose:** After administration of up to 10 times the recommended dose (2.5 mg/kg bw benazepril hydrochloride, 20 mg/kg bw spironolactone) to healthy dogs, dose dependant adverse effects were noted. Daily overdoses to healthy dogs, that is, 6 times (1.5 mg/kg bw benazepril hydrochloride and 12 mg/kg bw spironolactone) and 10 times (2.5 mg/kg bw benazepril hydrochloride and 20 mg/kg bw spironolactone) the recommended dose, led to a slight dose related decrease in red cell mass. However, this very slight decrease was transient, the red cell mass remained within the normal range, and the finding was not considered to be of clinical importance. A dose related but moderate compensatory physiological hypertrophy of the zona glomerulosa of the adrenal glands was also observed at doses of 3 times and greater of the recommended dose. This hypertrophy does not seem to be linked to any pathology and was observed to be reversible upon discontinuation of the treatment. In case of the accidental ingestion by a dog of many Cardalis tablets, there is no specific antidote or treatment. It is therefore recommended to induce vomiting and then carry out gastric lavage (depending on the risk assessment) and monitor electrolytes. Symptomatic treatment, e.g., fluid therapy, should also be provided. **Shelf life:** Shelf life of the veterinary medicinal product as packaged for sale: 2 years. Shelf life after first opening the bottle: 6 months. **Pharmaceutical precautions:** This veterinary medicinal product does not require any special storage conditions. Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements. Legal Category: **POM-V**

Why treat only
half the problem?

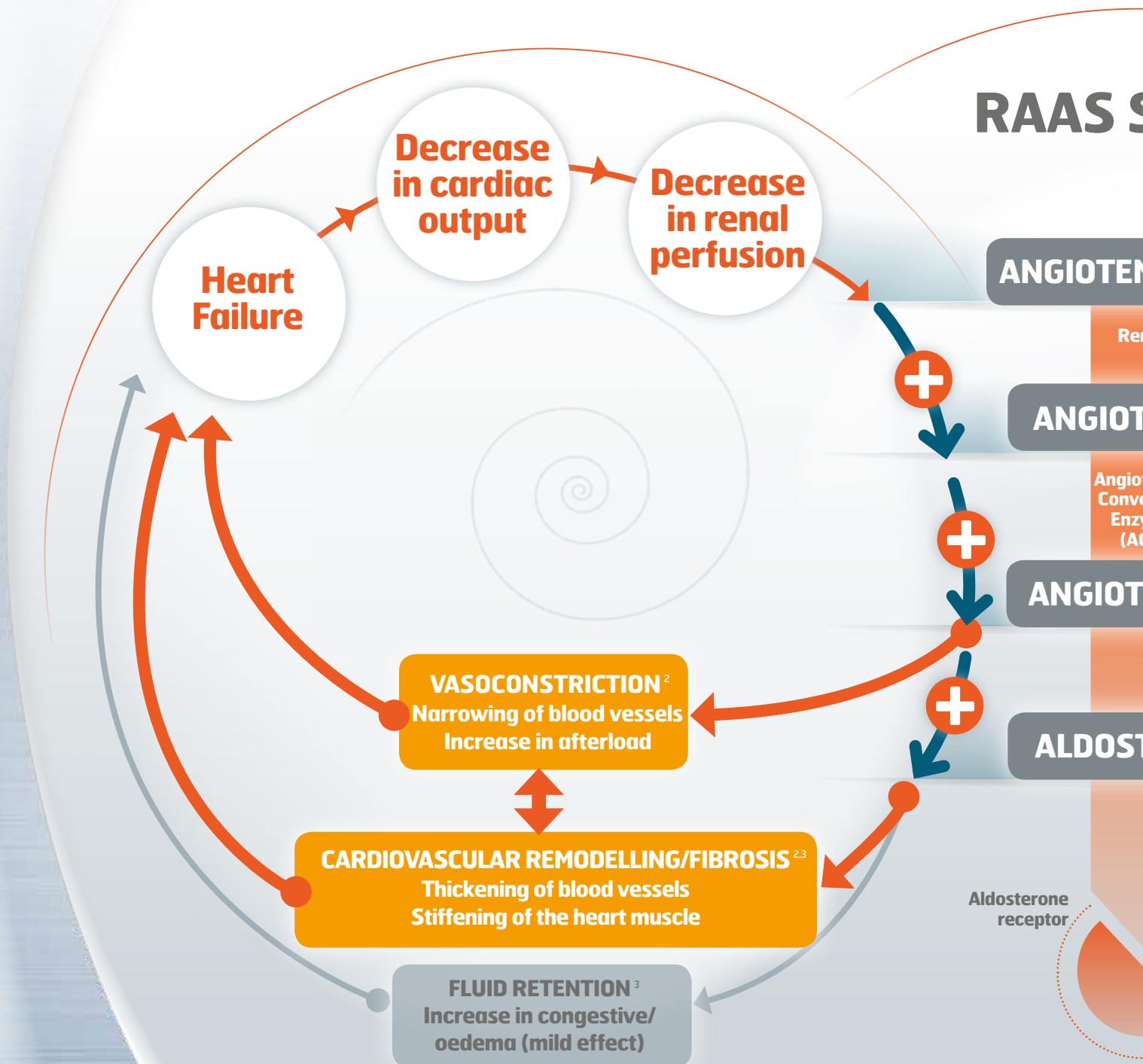


Cardalis[®]
Benazepril-Spironolactone
COMBINED FOR LIFE



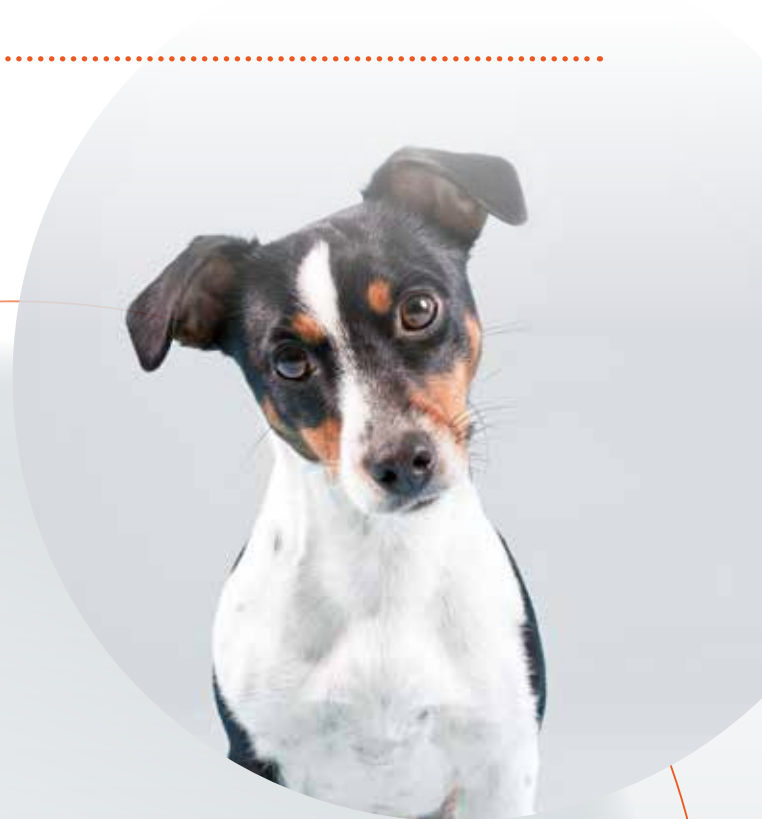
Angiotensin II and aldosterone

Heart failure causes activation of the RAAS System and the production of angiotensin II and aldosterone¹



Both angiotensin II and aldosterone have harmful effects which contribute to the vicious cycle of heart failure^{2,3}.

The importance of dual blockade



System

ANGIOTENSINOGEN

Angiotensin converting enzyme (ACE)

ANGIOTENSIN I

ANGIOTENSIN II

ALDOSTERONE

Other aldosterone stimulation factors
K⁺
ACTH
Furosemide



← ACE Inhibitor



← Spironolactone



ACE Inhibitors, such as benazepril, prevent the synthesis of angiotensin II²



Aldosterone levels, however, can continue to rise in patients receiving an ACE Inhibitor. This is because other factors also stimulate aldosterone production^{2,3,4,5,6,7}



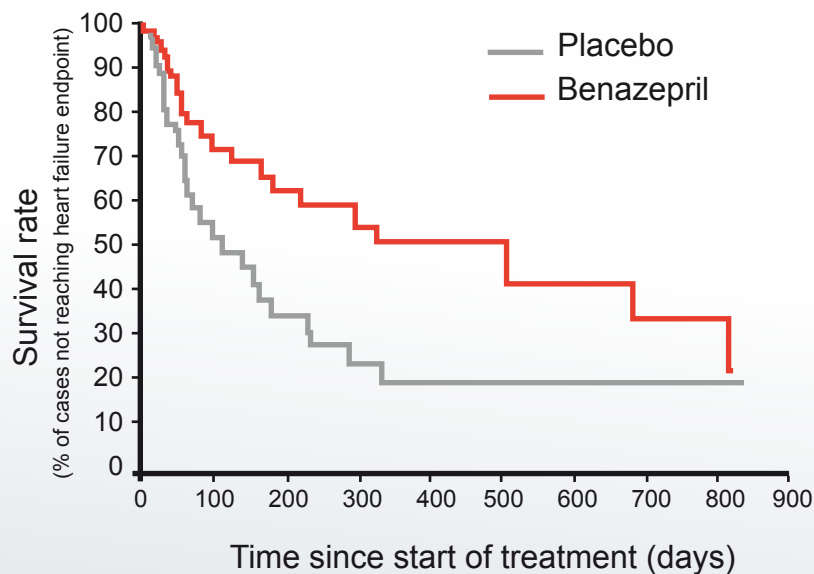
Spironolactone takes the place of aldosterone on its receptor and therefore blocks the harmful effects of aldosterone^{3,8}

Combining an ACE Inhibitor and spironolactone is the best strategy to achieve comprehensive blockade of the RAAS System^{2,3,8}.

Clinical evidence for the

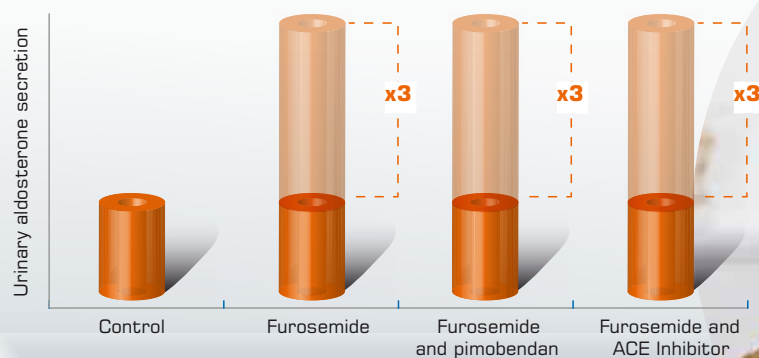
The benefits of **ACE Inhibitors** have been clearly demonstrated in clinical trials²:

- 🐾 Double-blind, placebo-controlled study looking at 125 dogs with heart failure caused by mitral valve disease
- 🐾 **49% reduction in the risk of mortality** when dogs received the leading ACE Inhibitor benazepril⁹



However, despite these benefits:

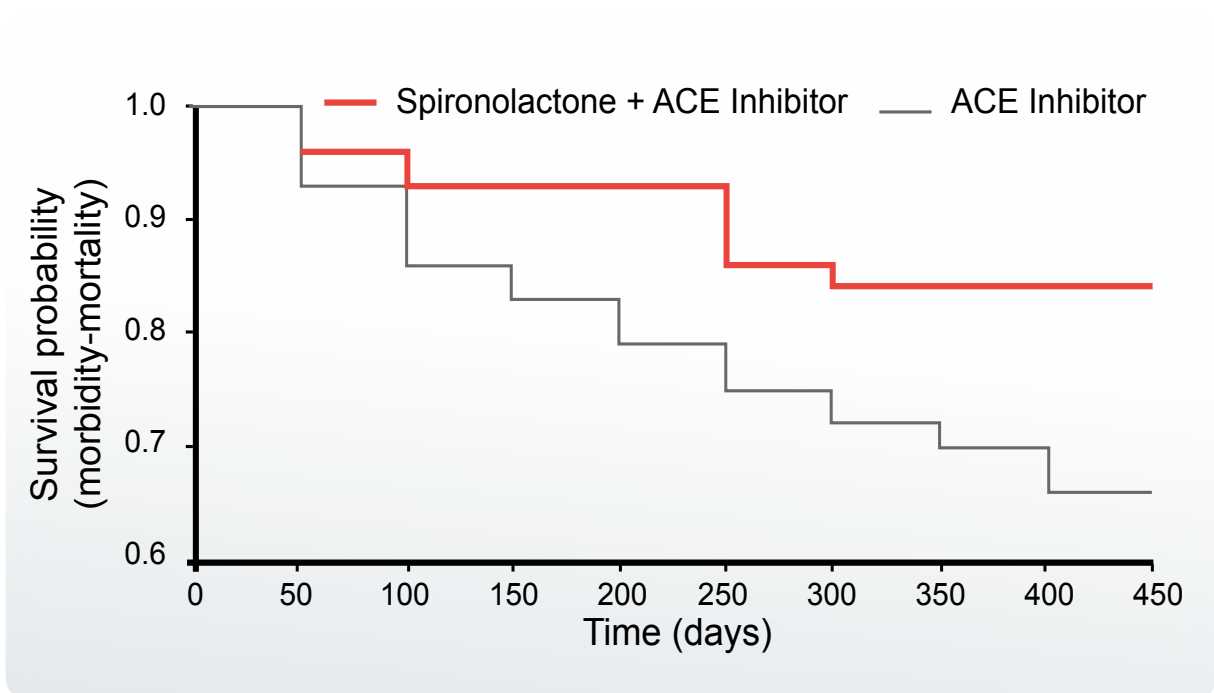
- 🐾 Aldosterone levels can continue to rise in heart failure patients receiving an ACE Inhibitor^{2,6}
- 🐾 In studies on healthy dogs, furosemide was shown to cause a three fold increase in aldosterone, an effect which was not inhibited by either an ACE Inhibitor or pimobendan^{4,5,7}



benefits of dual blockade

The efficacy of the aldosterone antagonist **spironolactone** is well established in veterinary cardiology²:

- Double-blind placebo-controlled study looking at 212 dogs with heart failure caused by mitral valve disease
- **69% reduction in the risk of mortality** when dogs received spironolactone in addition to an ACE Inhibitor⁸



- **Quality of life benefits:**
 - *Quicker improvement in cough and activity levels¹⁰*
 - *Slower deterioration of cough, heart sounds and appetite¹⁰*

The combination of benazepril and spironolactone has been shown to improve quality of life and prolong survival for dogs with heart failure^{10*}.

* For the home-care treatment of congestive heart failure caused by chronic degenerative valvular disease in dogs (with diuretic support as appropriate)

Cardalis®: the unique combination of benazepril and spironolactone



Two active ingredients combined at their standard dosage

- Benazepril
- Spironolactone

Easy to give

- Small, beef flavoured tablets
- Once daily administration with food

Easy to prescribe

- Three tablet sizes
- 30 tablets per pot

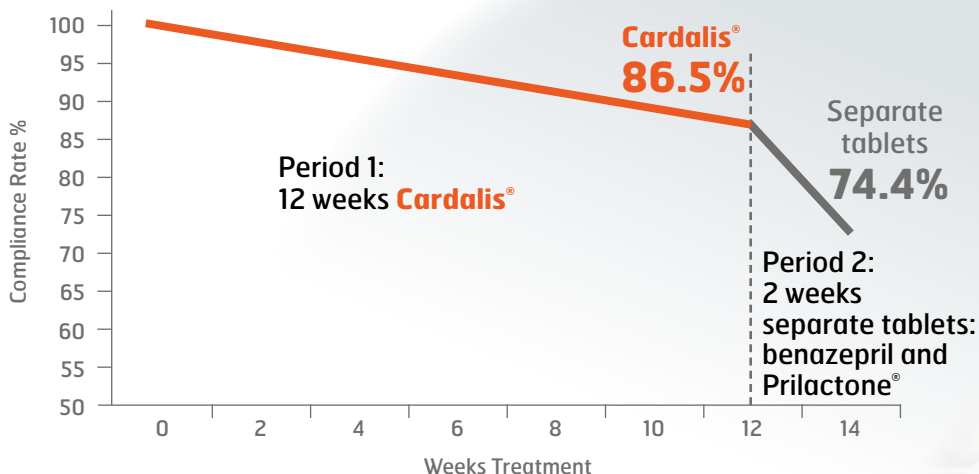
Dog bodyweight (kg)	2.5mg Benazepril 20mg Spironolactone	5mg Benazepril 40mg Spironolactone	10mg Benazepril 80mg Spironolactone
2.5 - 5	1/2		
5 - 10	1		
10 - 20		1	
20 - 40			1
40 - 60			1 + 1/2
60 - 80			2

Cardalis® should be given as part of your first-line heart failure therapy*.

* For the home-care treatment of congestive heart failure caused by chronic degenerative valvular disease in dogs (with diuretic support as appropriate)

Cardalis®: compliance and safety

In a field study involving 101 dogs, **Cardalis®** has been shown to **improve compliance...**



...and owner satisfaction".

Ease of administration confirmed by 97% of owners

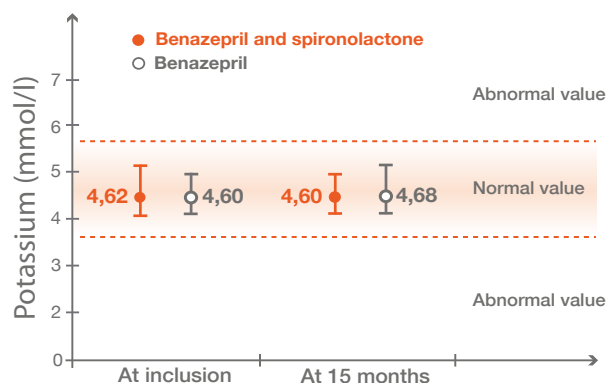
9 out of 10 dogs take the tablets spontaneously



Clinical studies have also demonstrated:

Comparable potassium levels for dogs receiving benazepril and spironolactone and those receiving benazepril alone^{10,*}

No clinically significant effects when administered to healthy dogs at up to 10 times the recommended dose^{10,12,13}



“Based on evidence-based medicine, there is justification for the use of all three categories of heart failure medications – ACE Inhibitors, pimobendan and spironolactone – alongside furosemide”¹⁴

Mike Martin MVB DVC MRCVS RCVS Cardiology Specialist

* For the treatment of congestive heart failure caused by chronic degenerative valvular disease in dogs (with diuretic support as appropriate). See datasheet on the back page for a full list of precautions. An increased incidence of hyperkalaemia was not observed in clinical trials performed in dogs with this combination. However, regular monitoring of renal function and serum potassium levels is recommended in dogs with renal impairment, as they may have an increased risk of hyperkalaemia. This should also be evaluated before initiating treatment, especially in dogs which may suffer hypoadrenocorticism, hyperkalaemia or hyponatraemia.