The unique combination of
benazepril and **spironolactone**

Cardalis®

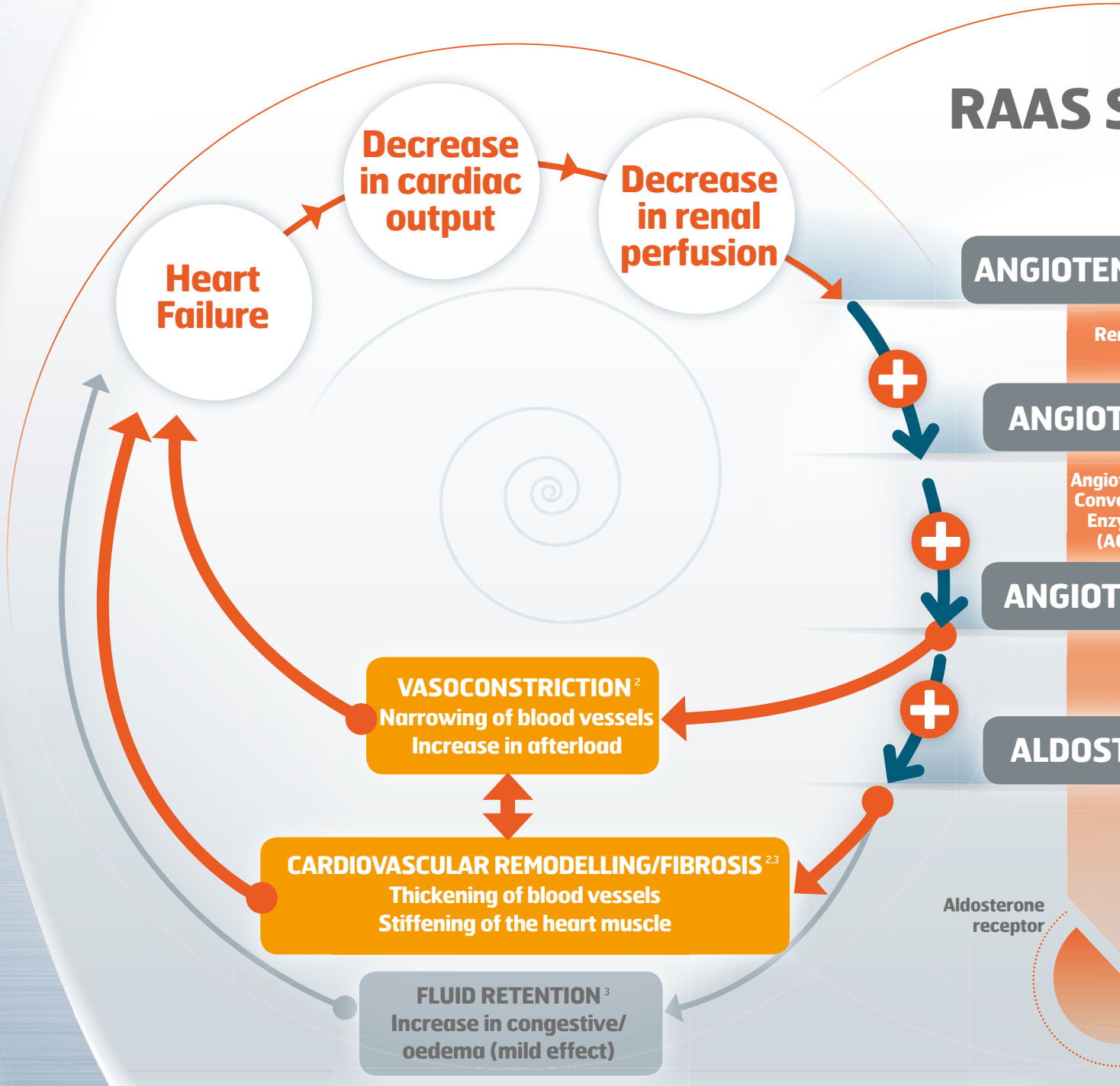
Benazepril-Spironolactone

COMBINED FOR LIFE

ceva

Angiotensin II and aldosterone

Heart failure causes activation of the RAAS System and the production of angiotensin II and aldosterone[1]



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

NSINOGEN

nin

TENSIN I

tensin
erting
yme
CE)

ACE Inhibitor

ENSIN II

Other aldosterone stimulation factors
K^+
ACTH
Furosemide

TERONE

Spironolactone

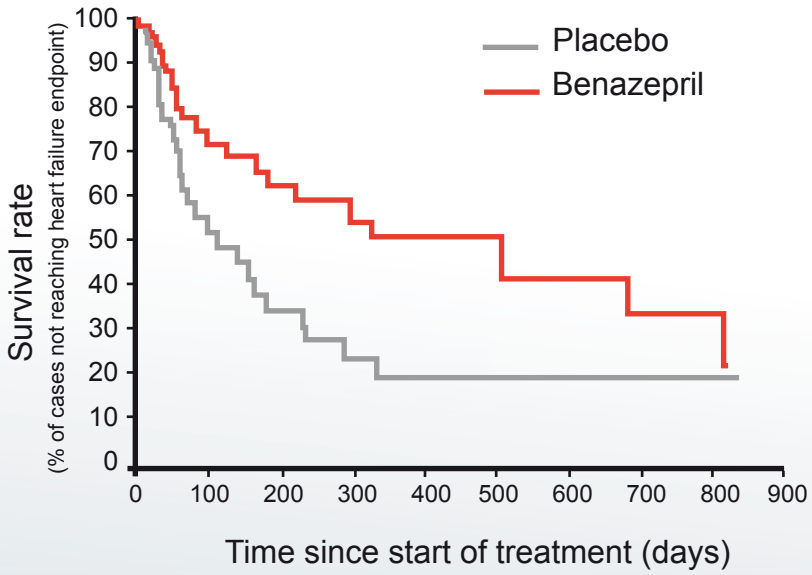
- **ACE Inhibitors,** such as benazepril, prevent the synthesis of angiotensin II[2]
- Aldosterone levels, however, can continue to rise in patients receiving an ACE Inhibitor. This is because other factors also stimulate aldosterone production[2,3,4,5,6,7]
- **Spironolactone** takes the place of aldosterone 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

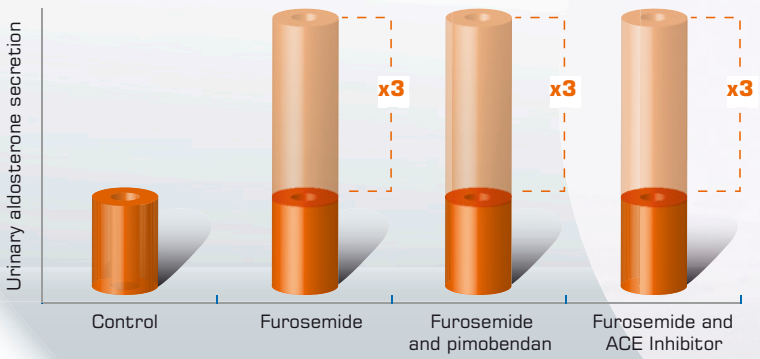
The benefits of **ACE Inhibitors** have been clearly demonstrated in clinical trials[2]:

- 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 benazepril[9]



However, despite these benefits:

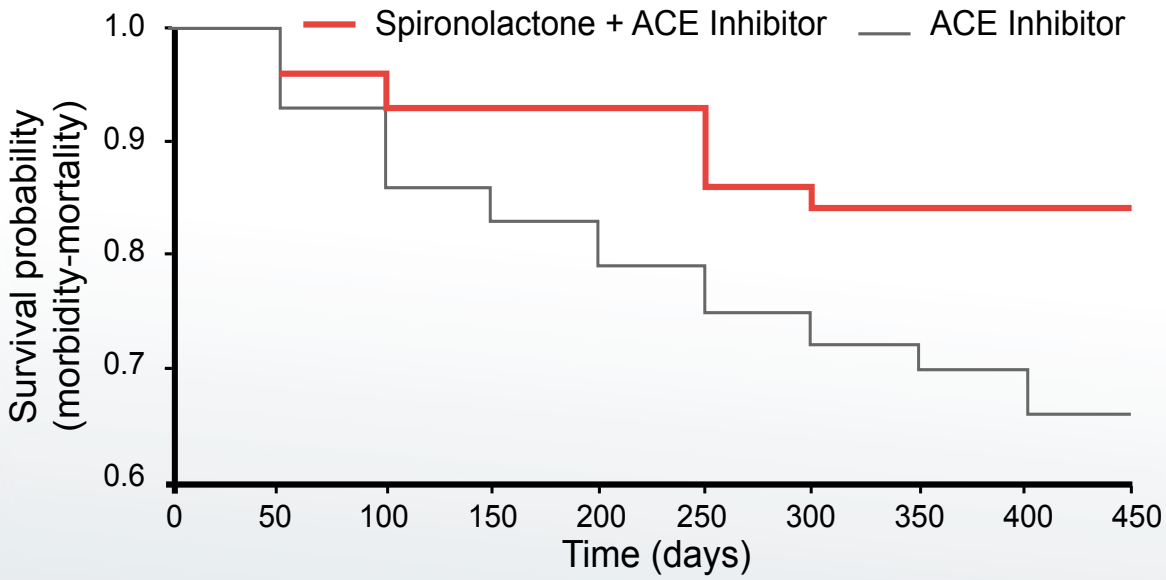
- Aldosterone levels can continue to rise in heart failure patients receiving an ACE Inhibitor[2,6]
- In studies on healthy dogs, furosemide was shown to cause a three fold increase in aldosterone, an effect which was not inhibited by either an ACE Inhibitor or pimobendan[4,5,7]



benefits of dual blockade

The efficacy of the aldosterone antagonist **spironolactone** is well established in veterinary cardiology[2]:

- 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 Inhibitor[8]



Furthermore, when looking specifically at dogs receiving spironolactone and benazepril (compared with benazepril alone):

- **89% reduction in the risk of mortality**[10]
- **Quality of life benefits:**
  - *Quicker improvement in cough and activity levels*[10]
  - *Slower deterioration of cough, heart sounds and appetite*[10]

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 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: 0.25mg/kg
- Spironolactone: 2mg/kg

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)	Cardalis Small 2.5mg Benazepril 20mg Spironolactone	Cardalis Medium 5mg Benazepril 40mg Spironolactone	Cardalis Large 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 instead of your usual ACE Inhibitor*.

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

Cardalis®: combined for life

"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 dogs with chronic heart failure caused by mitral valve disease requiring home-care, my approach is to use furosemide, ACE Inhibitor, pimobendan as well as spironolactone"[15]

Professor Clarke Atkins MDVM
ACVIM Cardiology Specialist

To find out more from leading experts about the management of heart failure in practice, visit the following free CPD website:

www.cardioacademy.cevalearn.com
1st international e-learning programme in cardiology

Each module lasts around 20-30 minutes. CPD certificates are then available upon completion. The website is updated on a regular basis and currently includes the following sessions:

Pathophysiology of mitral valve disease Cardiac biomarkers	Adrian Boswood
Clinical examination of the cardiac dog Compliance - a long term challenge	Gérard Le Bobinnec
Thoracic X-rays - how to proceed, normal features and abnormal features	Nicole Van Israël
Echocardiography - common views, mitral valve disease and and DCM	Anne French
Cardiac drugs - mechanism of action Management of mitral valve disease and DCM	Clarke Atkins
Cardiology Case Study	Jordi Lopez-Alvarez

Cardalis®: safety profile

Cardalis® has been assessed on the field in a 15 week study involving 101 dogs (furosemide and pimobendan were also authorised from inclusion)[11] .

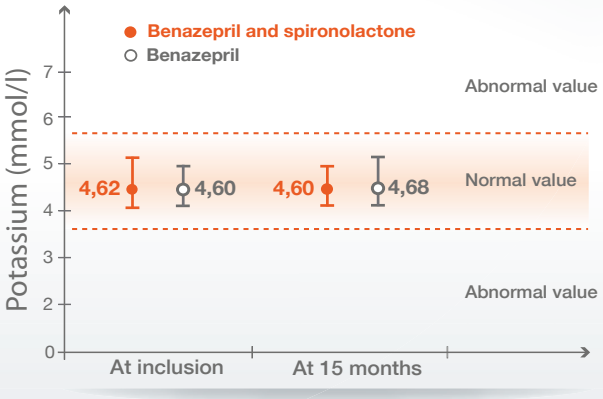
The dogs treated with this combination showed a quick clinical improvement from the first week and the study confirmed that Cardalis® was well tolerated when combined with:

- **Pimobendan**[12]
- **Furosemide**
  - Activates RAAS System[2,3,4,5,6,7]

* Improved: remains without the sign or improved compared to Day 0

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[10,13]



Cardalis® has a good safety profile*

* 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.

Cardalis®: ease of use

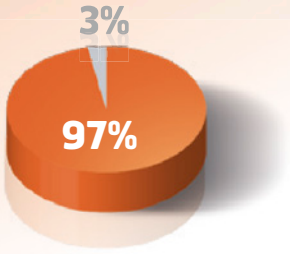
Heart failure is a chronic condition requiring polytherapy; compliance is therefore a key issue for vets and pet owners.

The preference for **Cardalis®** has been assessed in a field study involving 101 dogs[11] who were prescribed:

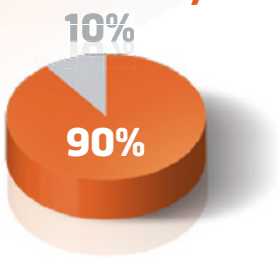
- **Cardalis®** for 3 months, followed by separate benazepril and spironolactone tablets for 2 weeks
- Furosemide and pimobendan were also authorised from inclusion

Dog owner preference

Ease of administration

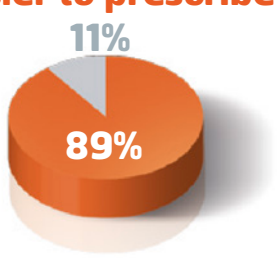


Palatability



Vets opinion

Easier to prescribe



Cardalis 2 separate tablets

Compliance

86.5%

fully complied with 3 months Cardalis® treatment regime

This dropped by 14% within 2 weeks of using the two separate actives

Cardalis® makes it easier for you to prescribe and your patients to benefit from benazepril and spironolactone as part of first-line heart failure therapy*.

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

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*.

Why should Cardalis® be administered with food?

Spironolactone is fat soluble and its absorption is increased by bile, which is produced following feeding. It has been shown that the absorption of spironolactone is 80-90% when administered with food versus 32-49% when given without food[10].

Can Cardalis® be used alongside pimobendan?

Yes, it has been shown that Cardalis® is well tolerated when combined with pimobendan[12]

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].

PRACTICE SUPPORT

Ceva Animal Health are able to provide a wide-range of practice support materials, including a waiting room poster and client information booklets. To receive this material, or if you have any further questions, please visit **www.ceva.com** or contact the **practice support team on (01494) 781510**.

* 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 enalepril or hydralazine on the rennin-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-occuring 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®), *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, *EAVPT 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 ß-blockers, calcium channels 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 deoxycorticosterone 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

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Use Medicines Responsibly (www.noah.co.uk/responsible)

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