ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cardalis 2.5 mg/20 mg chewable tablets for dogs
Cardalis 5 mg/40 mg chewable tablets for dogs
Cardalis 10 mg/80 mg chewable tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains:

Active substances:

	Benazepril hydrochloride (HCl) (benazeprilum HCl)	**Spironolactone** (spironolactonum)
Cardalis 2.5 mg/20 mg tablets	2.5 mg	20 mg
Cardalis 5 mg/40 mg tablets	5 mg	40 mg
Cardalis 10 mg/80 mg tablets	10 mg	80 mg

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.
Brown palatable oblong shaped chewable tablets with a score line.
The tablets can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

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

4.3 Contraindications

Do not use during pregnancy and lactation (see section 4.7).
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.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

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.
Reversible prostatic atrophy in entire male dogs treated with spironolactone was noted in a Target Animal Safety study at the recommended dose.

The product should be used with caution in dogs with hepatic dysfunction because it may alter the extensive biotransformation of spironolactone in liver.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

People with known hypersensitivity to spironolactone or benazepril should avoid contact with the 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.

Accidental ingestion, particularly by children, may lead to adverse events such as drowsiness, nausea and vomiting and diarrhoea, and skin rashes.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

Vomiting, diarrhoea,pruritus, lethargy, anorexia, ataxia, incoordination or signs of fatigue have been reported very rarely.
In dogs with chronic kidney disease, benazepril may increase plasma creatinine concentrations at the start of therapy very rarely. A moderate increase in plasma creatinine concentrations following administration of ACE inhibitors is compatible with the reduction in glomerular hypertension induced by these agents and is therefore not necessarily a reason to stop therapy in the absence of other signs.
The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))- common (more than 1 but less than 10 animals treated in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 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.

4.8 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 (see section 4.5).

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.

4.9 Amounts to be administered and administration route

This fixed combination product should only be used in dogs which require both active substances to be administered concomitantly at this fixed dose.

Oral use.

Cardalis chewable tablets should be administered to the dog once a day at a dosage of 0.25 mg/kg bodyweight (bw) benazepril hydrochloride (HCl) and 2 mg/kg bodyweight spironolactone, according to the following dosage table.

The tablets should be administered with food, either mixed with a small amount of food offered to the dog just prior to the main meal, or with the meal itself. The tablets contain beef flavouring to improve palatability, and in a field study conducted in dogs with chronic degenerative valvular disease the tablets were voluntarily and fully consumed 92% of the time when offered either with or without food.

Bodyweight (kg) of dog	Strength and number of tablets to be administered:		
	Cardalis 2.5 mg/20 mg chewable tablets	Cardalis 5 mg/40 mg chewable tablets	Cardalis 10 mg/80 mg chewable tablets
2.5 - 5	½		
5 - 10	1		
10 - 20		1	
20 - 40			1
40 - 60			1 + ½
60 - 80			2

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

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 (see section 4.6).

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 chewable 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.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, ACE inhibitors, combinations.
ATCvet code: QC09BA07.

5.1 Pharmacodynamic properties

Spironolactone and its active metabolites (including 7-α-thiomethyl-spironolactone and canrenone) act as specific antagonists of aldosterone by binding competitively to mineralocorticoid receptors located in the kidneys, heart and blood vessels. In the kidney, spironolactone inhibits the aldosterone-induced sodium retention leading to increase in sodium, and subsequently water excretion, and potassium retention. The resulting reduction in extracellular volume decreases the cardiac preload and left atrial pressure. The result is an improvement in heart function. In the cardiovascular system, spironolactone prevents the detrimental effects of aldosterone. Aldosterone promotes myocardial fibrosis, myocardial and vascular remodelling and endothelial dysfunction, although the precise mechanism of action is not yet clearly defined. In experimental models in dogs, it was shown that long term therapy with an

aldosterone antagonist prevents progressive left ventricle dysfunction and attenuates left ventricle remodelling in dogs with chronic heart failure.

Benazepril hydrochloride is a prodrug hydrolysed *in vivo* into its active metabolite, benazeprilat. Benazeprilat is a highly potent and selective inhibitor of angiotensin converting enzyme (ACE), thus preventing the conversion of inactive angiotensin I to active angiotensin II. Therefore, it blocks effects mediated by angiotensin II, including vasoconstriction of both arteries and veins, retention of sodium and water by the kidney.

The product causes a long-lasting inhibition of plasma ACE activity in dogs, with more than 95% inhibition at peak effect and significant activity (>80%) persisting 24 hours after dosing.

The association of spironolactone and benazepril is beneficial as both act on the renin-angiotensin-aldosterone system (RAAS) but at different levels along the cascade.

Benazepril, by preventing the formation of Angiotensin-II, inhibits the detrimental effects of vasoconstriction and stimulation of aldosterone release. However, aldosterone release is not fully controlled by ACE Inhibitors because Angiotensin-II is also produced by non-ACE pathways such as chymase (phenomenon known as “aldosterone breakthrough”). Secretion of aldosterone can also be stimulated by factors other than Angiotensin-II, notably K+ increase or ACTH. Therefore, to achieve a more complete inhibition of the deleterious effects of RAAS overactivity which occurs with heart failure, it is recommended to use aldosterone antagonists, such as spironolactone, concomitantly with ACE inhibitors to block specifically the activity of aldosterone (regardless of the source), through competitive antagonism on mineralocorticoid receptors. Clinical studies investigating the survival time demonstrated that the fixed combination increased the life expectancy in dogs with congestive heart failure with a 89% reduction in the relative risk of cardiac mortality assessed in dogs treated with spironolactone in combination with benazepril (as the hydrochloride) compared to dogs treated with benazepril (as hydrochloride) alone (mortality was classified as death or euthanasia due to heart failure). It also allowed a quicker improvement of cough and activity and a slower degradation of cough, heart sounds and appetite.

A slight increase in aldosterone blood levels may be observed in animals on treatment. This is thought to be due to activation of feedback mechanisms without adverse clinical consequence. There may be a dose related hypertrophy of the adrenal *zona glomerulosa* at high dose rates.In a field study conducted in dogs with chronic degenerative valvular disease 85.9% of dogs showed good compliance with treatment (≥90% of prescribed tablets successfully administered) over a three month period.

5.2 Pharmacokinetic particulars

The pharmacokinetics of spironolactone are based on its metabolites, as the parent compound is unstable at assay.

Absorption

After oral administration of spironolactone to dogs, it was demonstrated that the three metabolites achieved levels of 32 to 49% of the administered dose. Food increases the bioavailability to 80 to 90%. Following oral administration of 2 to 4 mg/kg, absorption increases linearly over the range.

After multiple oral doses of 2 mg spironolactone per kg (with 0.25 mg benazepril hydrochloride per kg) for 7 consecutive days, no accumulation is observed. At steady state, mean C_{max} of 324 µg/l and 66 µg/l are achieved for the primary metabolites, 7-α-thiomethyl-spironolactone and canrenone, 2 and 4 hours post-dosing, respectively. Steady-state conditions are reached by day 2.

After oral administration of benazepril hydrochloride, peak levels of benazepril are attained rapidly and decline quickly as the drug is partially metabolized by liver enzymes to benazeprilat. Unchanged

benazepril and hydrophilic metabolites account for the remainder. The systemic bioavailability of benazepril is incomplete due to incomplete absorption and first pass metabolism. There is no significant difference in the pharmacokinetics of benazeprilat when benazepril (as hydrochloride) is administered to fed or fasted dogs.

After multiple oral doses of 0.25 mg benazepril hydrochloride per kg (with 2 mg spironolactone per kg) for 7 consecutive days, a peak benazeprilat concentration (C_{max} of 52.4 ng/ml) is achieved with a T_{max} of 1.4 h.

Distribution

The mean volumes of distribution of 7-α-thiomethyl-spironolactone and canrenone are approximately 153 litres and 177 litres respectively. The mean residence time of the metabolites ranges from 9 to 14 hours and they are preferentially distributed to the gastro-intestinal tract, kidney, liver and adrenal glands.

Benazepril and benazeprilat are rapidly distributed, mainly in liver and kidney.

Biotransformation

Spironolactone is rapidly and completely metabolised by the liver into its active metabolites, 7α-thiomethyl-spironolactone and canrenone, which are the primary metabolites in the dog. After co-administration of spironolactone (2 mg/kg bw) and benazepril hydrochloride (0.25 mg/kg bw) the terminal plasma half-lives ($t_{½}$) were 7 hours and 6 hours for canrenone and 7-α-thiomethyl-spironolactone respectively.

Benazeprilat concentrations decline biphasically: the initial fast phase represents elimination of free drug, while the terminal phase reflects the release of benazeprilat that was bound to ACE, mainly in the tissues. After co-administration of spironolactone (2 mg/kg bw) and benazepril hydrochloride (0.25 mg/kg bw) the terminal plasma half-life of benazeprilat ($t_{½}$) was 18 hours. Benazepril and benazeprilat are extensively bound to plasma proteins, and in tissues are found mainly in the liver and kidney.

Repeated administration of benazepril leads to slight bioaccumulation of benazeprilat, steady state being achieved within few days.

Elimination

Spironolactone is mainly excreted via its metabolites. The plasma clearances of canrenone and 7-α-thiomethyl-spironolactone are 1.5 l/h/kg bw and 0.9 l/h/kg bw respectively. After the oral administration of radiolabelled spironolactone to the dog, 70% of the dose is recovered in faeces and 20% in the urine.

Benazeprilat is excreted via the biliary and the urinary route in dogs. The clearance of benazeprilat is not affected in dogs with impaired renal function and therefore no adjustment of benazepril dose is required in cases of renal insufficiency

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose microcrystalline
Povidone K30

Artificial beef flavour
Compressible sugar
Crospovidone
Magnesium stearate

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the bottle: 6 months.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

White plastic (HDPE) bottle with a child-resistant closure in a cardboard box.

Pack sizes of 30 or 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Ceva Santé Animale
10, av. de la Ballastière
33500 Libourne
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/12/142/001(1 x 30 tablets, 2.5 mg/20 mg)
EU/2/12/142/002 (1 x 90 tablets, 2.5 mg/20 mg)
EU/2/12/142/003 (1 x 30 tablets, 5 mg/40 mg)
EU/2/12/142/004 (1 x 90 tablets, 5 mg/40 mg)
EU/2/12/142/005 (1 x 30 tablets, 10 mg/80 mg)
EU/2/12/142/006 (1 x 90 tablets, 10 mg/80 mg)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23/07/2012
Date of latest renewal: 08/06/2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agencyhttp://www.ema.europa.eu

PROHIBITION OF SALE, SUPPLY AND/OR USE
Not applicable.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. STATEMENT OF THE MRLs

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Ceva Santé Animale
Z.I. Tres le Bois
22600 Loudeac
France

Catalent Germany Schorndorf GmbH
Steinbeisstrasse 2
D-73614 Schorndorf
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box of 1 bottle of 30 tablets
Cardboard box of 1 bottle of 90 tablets

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cardalis 2.5 mg/20 mg chewable tablets for dogs
Cardalis 5 mg/40 mg chewable tablets for dogs
Cardalis 10 mg/80 mg chewable tablets for dogs

benazepril HCl/spironolactone

2. STATEMENT OF ACTIVE SUBSTANCES

benazepril HCl 2.5 mg, spironolactone 20 mg
benazepril HCl 5 mg, spironolactone 40 mg
benazepril HCl 10 mg, spironolactone 80 mg

3. PHARMACEUTICAL FORM

Chewable tablet

4. PACKAGE SIZE

30 tablets
90 tablets

5. TARGET SPECIES

Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once opened, use within 6 months.

11. SPECIAL STORAGE CONDITIONS

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Read the package leaflet before use.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ceva Santé Animale
10 av. de La Ballastière
33500 Libourne
France

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/12/142/001 (1 x 30 tablets 2.5 mg/20 mg)
EU/2/12/142/002 (1 x 90 tablets 2.5 mg/20 mg)
EU/2/12/142/003 (1 x 30 tablets 5 mg/40 mg)
EU/2/12/142/004 (1 x 90 tablets 5 mg/40 mg)
EU/2/12/142/005 (1 x 30 tablets 10 mg/80 mg)
EU/2/12/142/006 (1 x 90 tablets 10 mg/80 mg)

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Bottle of 30 tablets
Bottle of 90 tablets

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cardalis 2.5 mg/20 mg chewable tablets for dogs
Cardalis 5 mg/40 mg chewable tablets for dogs
Cardalis 10 mg/80 mg chewable tablets for dogs

benazepril HCl/spironolactone

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

benazepril HCl 2.5 mg, spironolactone 20 mg
benazepril HCl 5 mg, spironolactone 40 mg
benazepril HCl 10 mg, spironolactone 80 mg

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

30 tablets
90 tablets

4. ROUTE(S) OF ADMINISTRATION

5. WITHDRAWAL PERIOD(S)

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Cardalis 2.5 mg/20 mg chewable tablets for dogs
Cardalis 5 mg/40 mg chewable tablets for dogs
Cardalis 10 mg/80 mg chewable tablets for dogs

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
Ceva Santé Animale
10, av. de La Ballastière
33500 Libourne
France

Manufacturers responsible for batch release:
Ceva Santé Animale
Z.I. Très le Bois
22600 Loudéac
France

Catalent Germany Schorndorf GmbH
Steinbeisstrasse 2
73614 Schorndorf
Germany

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cardalis 2.5 mg/20 mg chewable tablets for dogs
Benazepril hydrochloride 2.5 mg, spironolactone 20 mg

Cardalis 5 mg/40 mg chewable tablets for dogs
Benazepril hydrochloride 5 mg, spironolactone 40 mg

Cardalis 10 mg/80 mg chewable tablets for dogs
Benazepril hydrochloride 10 mg, spironolactone 80 mg

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each chewable tablet contains:

	Benazepril hydrochloride (HCl) (benazeprilum HCl)	**Spironolactone (**spironolactonum**)**
Cardalis 2.5 mg/20 mg tablets	2.5 mg	20 mg
Cardalis 5 mg/40 mg tablets	5 mg	40 mg
Cardalis 10 mg/80 mg tablets	10 mg	80 mg

The tablets are brown coloured, palatable, oblong shaped with a score line and chewable.

4. INDICATION

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

5. CONTRAINDICATIONS

Do not use during pregnancy and lactation (see section "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.

6. ADVERSE REACTIONS

Vomiting, diarrhoea,pruritus, lethargy, anorexia, ataxia, incoordination or signs of fatigue have been reported very rarely.
In dogs with chronic kidney disease, benazepril may increase plasma creatinine concentrations at the start of therapy very rarely. A moderate increase in plasma creatinine concentrations following administration of ACE inhibitors is compatible with the reduction in glomerular hypertension induced by these agents and is therefore not necessarily a reason to stop therapy in the absence of other signs.
The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s)) - common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

This fixed combination product should only be used in dogs which require both active substances to be administered concomitantly at this fixed dose.

Oral use.

Cardalis chewable tablets should be administered to the dog once a day at a dosage of 0.25 mg/kg bodyweight benazepril hydrochloride (HCl) and 2 mg/kg bodyweight (bw) spironolactone, according to the following dosage table.

Bodyweight (kg) of dog	Strength and number of tablets to be administered:		
	Cardalis 2.5 mg/20 mg chewable tablets	Cardalis 5 mg/40 mg chewable tablets	Cardalis 10 mg/80 mg chewable tablets
2.5 - 5	½		
5 - 10	1		
10 - 20		1	
20 - 40			1
40 - 60			1 + ½
60 - 80			2

9. ADVICE ON CORRECT ADMINISTRATION

The tablets should be administered either mixed with a small amount of food offered to the dog just prior to the main meal, or with the meal itself. The tablets contain beef flavouring to improve palatability, and in a field study conducted in dogs with chronic degenerative valvular disease the tablets were voluntarily and fully consumed 92% of the time when offered either with or without food.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE CONDITIONS

Keep out of the sight and reach of children.

This veterinary medicinal product does not require any special storage conditions.

Do not use this veterinary medicinal product after the expiry date which is stated on the bottle.

Shelf-life after first opening the bottle: 6 months.

12. SPECIAL WARNING(S)

Special precautions for use in animals
Kidney function and serum potassium levels should be evaluated before initiating the treatment with benazepril (hydrochloride) 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.
Reversible prostatic atrophy in entire male dogs treated with spironolactone was noted in a Target Animal Safety study at the recommended dose.

The product should be used with caution in dogs with hepatic dysfunction because it may alter the extensive biotransformation of spironolactone in liver.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

People with known hypersensitivity to spironolactone or benazepril should avoid contact with the 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.

Accidental ingestion, particularly by children, may lead to adverse events such as drowsiness, nausea and vomiting and diarrhoea, and skin rashes.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Wash hands after use.

Pregnancy and lactation

Do not use during pregnancy and lactation. Embryotoxic effects (foetal urinary tract malformation) were seen in trials of benazepril (as hydrochloride) 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 the 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 (see section "Special precautions for use in animals").
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 (symptoms, emergency procedures, antidotes)

After administration of up to 10 times the recommended dose (2.5 mg/kg bw benazepril hydrochloride, 20 mg/kg spironolactone) to healthy dogs, dose dependent adverse effects were noted, see section "Adverse reactions".
Daily overdoses to healthy dogs, i.e. 6 times (1.5 mg/kg bw benazepril hydrochloride, 12 mg/kg bw spironolactone) and 10 times (2.5 mg/kg bw benazepril hydrochloride, 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 *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 chewable 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.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIAL, IF ANY

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

15. OTHER INFORMATION

Pack sizes
The tablets are packed bottles of 30 tablets or 90 tablets, and each bottle is presented in an outer cardboard box. The bottles are fitted with childproof caps.

Not all pack sizes may be marketed.

Pharmacodynamic properties
Spironolactone and its active metabolites (including 7-α-thiomethyl-spironolactone and canrenone) act as specific antagonists of aldosterone by binding competitively to mineralocorticoid receptors located in the kidneys, heart and blood vessels. In the kidney, spironolactone inhibits the aldosterone-induced sodium retention leading to increase in sodium, and subsequently water excretion, and potassium retention. The resulting reduction in extracellular volume decreases the cardiac preload and left atrial pressure. The result is an improvement in heart function. In the cardiovascular system, spironolactone prevents the detrimental effects of aldosterone. Aldosterone promotes myocardial fibrosis, myocardial and vascular remodelling and endothelial dysfunction, although the precise mechanism of action is not yet clearly defined. In experimental models in dogs, it was shown that long term therapy with an aldosterone antagonist prevents progressive left ventricle dysfunction and attenuates left ventricle remodelling in dogs with chronic heart failure.
Benazepril hydrochloride is a prodrug hydrolysed *in vivo* into its active metabolite, benazeprilat. Benazeprilat is a highly potent and selective inhibitor of angiotensin converting enzyme (ACE), thus preventing the conversion of inactive angiotensin I to active angiotensin II. Therefore, it blocks effects mediated by angiotensin II, including vasoconstriction of both arteries and veins, retention of sodium and water by the kidney.
The product causes a long-lasting inhibition of plasma ACE activity in dogs, with more than 95% inhibition at peak effect and significant activity (>80%) persisting 24 hours after dosing.
The association of spironolactone and benazepril is beneficial as both act on the renin-angiotensin-aldosterone system (RAAS) but at different levels along the cascade.
Benazepril, by preventing the formation of Angiotensin-II, inhibits the detrimental effects of vasoconstriction and stimulation of aldosterone release. However, aldosterone release is not fully controlled by ACE Inhibitors because Angiotensin-II is also produced by non-ACE pathways such as chymase (phenomenon known as “aldosterone breakthrough”). Secretion of aldosterone can also be stimulated by factors other than Angiotensin-II, notably K+ increase or ACTH. Therefore, to achieve

a more complete inhibition of the deleterious effects of RAAS overactivity which occurs with heart failure, it is recommended to use aldosterone antagonists, such as spironolactone, concomitantly with ACE inhibitors to block specifically the activity of aldosterone (regardless of the source), through competitive antagonism on mineralocorticoid receptors. Clinical studies investigating the survival time demonstrated that the fixed combination increased the life expectancy in dogs with congestive heart failure with a 89% reduction in the relative risk of cardiac mortality assessed in dogs treated with spironolactone in combination with benazepril (hydrochloride) compared to dogs treated with benazepril (hydrochloride) alone (mortality was classified as death or euthanasia due to heart failure). It also allowed a quicker improvement of cough and activity and a slower degradation of cough, heart sounds and appetite.
A slight increase in aldosterone blood levels may be observed in animals on treatment. This is thought to be due to activation of feedback mechanisms without adverse clinical consequence. There may be a dose related hypertrophy of the adrenal *zona glomerulosa* at high dose rates.In a field study conducted in dogs with chronic degenerative valvular disease 85.9% of dogs showed good compliance with treatment (≥ 90% of prescribed tablets successfully administered) over a three month period.