ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances:

Each tablet contains:

<table>
<thead>
<tr>
<th></th>
<th>S. 2.5 mg/20 mg tablets</th>
<th>S. 5 mg/40 mg tablets</th>
<th>S. 10 mg/80 mg tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril</td>
<td>2.5 mg</td>
<td>5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>hydrochloride (HCl)</td>
<td>(benazeprili HCl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>20 mg</td>
<td>40 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>(spironolactonum)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Brown oblong shaped 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

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.

To be used with caution to treat 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

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.

4.6 Adverse reactions (frequency and seriousness)

A reversible prostatic atrophy is often observed in entire male dogs treated with spironolactone.

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 β-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 tablets should be administered to the dog once a day using 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.

<table>
<thead>
<tr>
<th>Bodyweight (kg) of dog</th>
<th>Strength and number of tablets to be administered:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardalis 2.5 mg/20 mg tablets</td>
</tr>
<tr>
<td>2.5 - 5</td>
<td>½</td>
</tr>
<tr>
<td>5 - 10</td>
<td>1</td>
</tr>
<tr>
<td>10 - 20</td>
<td>1</td>
</tr>
<tr>
<td>20 - 40</td>
<td>1</td>
</tr>
<tr>
<td>40 - 60</td>
<td>1 + ½</td>
</tr>
<tr>
<td>60 - 80</td>
<td></td>
</tr>
</tbody>
</table>

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 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

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: 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 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.

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 $C_{\text{max}}$ of 324 μg/l and 66 μg/l are achieved for the primary metabolites, 7-$\alpha$-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 ($C_{\text{max}}$ of 52.4 ng/ml) is achieved with a $T_{\text{max}}$ of 1.4 h.

Distribution

The mean volumes of distribution of 7-$\alpha$-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.

Metabolism

Spironolactone is rapidly and completely metabolised by the liver into its active metabolites, 7-$\alpha$-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 ($t_{\text{1/2}}$) were 7 hours and 6 hours for canrenone and 7-$\alpha$-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 ($t_{\text{1/2}}$) 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 **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)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

DD/MM/YYYY

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this product is available on the website of the European Medicines Agency (EMA) http://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

D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION
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 Loudéac
France

Catalent Germany Schorndorf GmbH
Steinbeisstrasse 2
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.

D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

Pharmacovigilance system

The marketing authorisation holder must ensure that the system of pharmacovigilance, as described in Part 1 of the marketing authorisation application, is in place and functioning before and whilst the product is on the market.

- CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable

- SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

None.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardboard box of 1 bottle of 30 tablets</td>
</tr>
<tr>
<td>Cardboard box of 1 bottle of 90 tablets</td>
</tr>
</tbody>
</table>

1. **NAME OF THE VETERINARY MEDICINAL PRODUCT**

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

   benazepril HCl/spironolactone

2. **STATEMENT OF ACTIVE AND OTHER 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**

   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**
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 REACH AND SIGHT OF CHILDREN”

Keep out of the reach and sight 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/0/00/000/000 30 tablets
EU/0/00/000/000 90 tablets
EU/0/00/000/000 30 tablets
EU/0/00/000/000 90 tablets
EU/0/00/000/000 30 tablets
EU/0/00/000/000 90 tablets
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 tablets for dogs
Cardalis 5 mg/40 mg tablets for dogs
Cardalis 10 mg/80 mg 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

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

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

Manufacturers for the 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 tablets for dogs
Benazepril hydrochloride 2.5 mg, spironolactone 20 mg

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

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

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

Cardalis is a brown coloured, palatable, oral tablet, oblong in shape and scored.

<table>
<thead>
<tr>
<th></th>
<th>Benazepril hydrochloride (HCl)</th>
<th>Spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardalis 2.5 mg/20 mg tablets</td>
<td>2.5 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Cardalis 5 mg/40 mg tablets</td>
<td>5 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Cardalis 10 mg/80 mg tablets</td>
<td>10 mg</td>
<td>80 mg</td>
</tr>
</tbody>
</table>
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 "Use during pregnancy, lactation or lay").
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

A reversible prostatic atrophy is often observed in entire male dogs treated with spironolactone.

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

<table>
<thead>
<tr>
<th>Bodyweight (kg) of dog</th>
<th>Strength and number of tablets to be administered:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardalis 2.5 mg/20 mg tablets</td>
</tr>
<tr>
<td></td>
<td>Cardalis 5 mg/40 mg tablets</td>
</tr>
<tr>
<td></td>
<td>Cardalis 10 mg/80 mg tablets</td>
</tr>
<tr>
<td>2.5 - 5</td>
<td>½</td>
</tr>
<tr>
<td>5 - 10</td>
<td>1</td>
</tr>
<tr>
<td>10 - 20</td>
<td>1</td>
</tr>
<tr>
<td>20 - 40</td>
<td>1</td>
</tr>
<tr>
<td>40 - 60</td>
<td>1 + ½</td>
</tr>
<tr>
<td>60 - 80</td>
<td>2</td>
</tr>
</tbody>
</table>
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.

10. **WITHDRAWAL PERIOD**

11. **SPECIAL STORAGE CONDITIONS**

Keep out of the reach and sight of children.  
Cardalis does not require any special storage conditions.  
Do not use after the expiry date 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.

To be used with caution to treat 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**

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.

**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 (as hydrochloride) with laboratory animals (rats) at maternally non-toxic doses.
**Interactions**

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 β-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**

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 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 product is available on the website of the European Medicines Agency (EMA) [http://www.ema.europa.eu](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.