ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

NL: Benazepril hydrochloride 5 mg tabletten voor honden
DE: Benakor 5 mg
DK: Benakor vet. 5 mg
EL: Benakor 5 mg ταμπλέτα για σκύλους
HU: Benakor 5 mg tabletta kutya részére A.U.V.
SE: Benakor vet. 5 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Active substance:
Benazepril hydrochloride 5 mg

Excipient:
Colourant: Iron oxides (E172) 0.5 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.
Yellow oblong divisible tablets, with a break mark on both sides.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications for use, specifying the target species

Treatment of congestive heart failure.

4.3 Contraindications

Do not use in case of hypersensitivity to the active substance or to any of the excipients.
Do not use in cases of hypotension, hypovolaemia, hyponatraemia or acute renal failure.
Do not use in cases of cardiac output failure due to aortic or pulmonary stenosis.
Do not use during pregnancy or lactation (section 4.7)

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

No evidence of renal toxicity to the product has been observed in dogs during clinical trials, however, as is routine in cases of chronic kidney disease, it is recommended to monitor plasma creatinine, urea and erythrocyte counts during therapy.

The efficacy and safety of the product has not been established in dogs below 2.5 kg body weight.

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

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

Pregnant women should take special care to avoid accidental oral exposure because angiotensin converting enzyme (ACE) inhibitors have been found to affect the unborn child during pregnancy in humans.

4.6 Adverse reactions (frequency and seriousness)

In double-blind clinical trials in dogs with congestive heart failure, benazepril hydrochloride was well tolerated with an incidence of adverse reactions lower than observed in placebo-treated dogs.

A small number of dogs may exhibit transient vomiting, incoordination or signs of fatigue.

In dogs with chronic kidney disease, the product may increase plasma creatinine concentrations at the start of therapy. 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.

4.7 Use during pregnancy, lactation or lay

Do not use during pregnancy or lactation. The safety of the product has not been established in breeding, pregnant or lactating dogs. Embryotoxic effects (foetal urinary tract malformation) were seen in trials with laboratory animals (rats) at maternally nontoxic doses.

4.8 Interaction with other medicinal products and other forms of interaction

In dogs with congestive heart failure, benazepril hydrochloride has been given in combination with digoxin, diuretics, pimobendan and anti-arrhythmic veterinary medicinal products without demonstrable adverse interactions.

In humans, the combination of ACE inhibitors and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) can lead to reduced antihypertensive efficacy or impaired renal function. The combination of benazepril hydrochloride and other antihypertensive agents (e.g. calcium channel blockers, β-blockers or diuretics), anaesthetics or sedatives may lead to additive hypotensive effects. Therefore, concurrent use of NSAIDs or other medications with a hypotensive effect should be considered with care. Renal function and signs of hypotension (lethargy, weakness etc.) should be monitored closely and treated as necessary.
Interactions with potassium preserving diuretics like spironolactone, triamterene or amiloride cannot be ruled out. It is recommended to monitor plasma potassium levels when using benazepril hydrochloride in combination with a potassium sparing diuretic because of the risk of hyperkalaemia.

4.9 Amounts to be administered and administration route

The product should be given orally once daily, with or without food. The duration of treatment is unlimited.

The product should be administered orally at a minimum dose of 0.25 mg (range 0.25-0.5) benazepril hydrochloride/kg body weight once daily, according to the following table:

Weight of dog (kg)	Benazepril hydrochloride 5 mg tabletten voor honden

	Standard dose	Double dose
>5-10	0.5 tablet	1 tablet
>10-20	1 tablet	2 tablets

The dose may be doubled, still administered once daily, to a minimum dose of 0.5 mg/kg (range 0.5-1.0), if judged clinically necessary and advised by the veterinary surgeon.

In case of using halved tablets: Put the remaining half of a divided tablet back in the blister pocket and store it in a dry place below 25ºC. Use the remaining tablet half for the next administration.

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

Benazepril hydrochloride reduced erythrocyte counts in normal dogs when dosed at 150 mg/kg body weight once daily for 12 months, but this effect was not observed at the recommended dose during clinical trials in dogs.
Transient reversible hypotension may occur in cases of accidental overdose. Therapy should consist of intravenous infusion of warm isotonic saline.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: ACE inhibitors, plain
ATCvet code: QC09AA07

5.1 Pharmacodynamic properties

Benazepril hydrochloride is a pro-drug hydrolysed in vivo to its active metabolite, benazeprilat. Benazeprilat is a highly potent and selective inhibitor of ACE, thus preventing the conversion of inactive angiotensin I to active angiotensin II and thereby also reducing synthesis of aldosterone. Therefore, it blocks effects mediated by angiotensin II and aldosterone, including vasoconstriction of both arteries and veins, retention of sodium and water by the kidney and remodelling effects (including pathological cardiac hypertrophy and degenerative renal changes).

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

The product reduces the blood pressure and volume load on the heart in dogs with congestive heart failure.

5.2 Pharmacokinetic particulars

After oral administration of benazepril hydrochloride, peak levels of benazepril are attained rapidly (T_{max} 1.1 hours in dogs) and decline quickly as the active substance is partially metabolised by liver enzymes to benazeprilat. The systemic bioavailability is incomplete (~13% in dogs) due to incomplete absorption (38% in dogs) and first pass metabolism. In dogs, peak benazeprilat concentrations (C_{max} of 384.16 ng/ml after a dose of 1.6 mg/kg benazepril hydrochloride) are achieved with a T_{max} of 1.1 hours.

Benazeprilat concentrations decline biphasically: the initial fast phase (t1/2=1.7 hours in dogs) represents elimination of free drug, while the terminal phase (t1/2=19 hours in dogs) reflects the release of benazeprilat that was bound to ACE, mainly in the tissues.

Benazepril and benazeprilat are extensively bound to plasma proteins (85-90%), and in tissues are found mainly in the liver and kidney.

There is no significant difference in the pharmacokinetics of benazeprilat when benazepril hydrochloride is administered to fed or fasted dogs. Repeated administration of benazepril hydrochloride leads to slight accumulation of benazeprilat (R=1.47 in dogs with 0.5 mg/kg), steady state being achieved within a few days (4 days in dogs).

Benazeprilat is excreted 54% via the biliary and 46% via the urinary route in dogs. The clearance of benazeprilat is not affected in dogs with impaired renal function and therefore no adjustment of benazepril hydrochloride dose is required in cases of renal insufficiency.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica colloidal anhydrous (E551)
Microcrystalline cellulose (E460)
Lactose anhydrous
Colorcon Pigment Blend 22870 yellow (Iron oxides, E172)
Sodium cyclamate (E952)
Sodium starch glycolate Type A
Magnesium stearate (E470b).

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale:
PVC/PE/PVDC-Aluminium blister: 12 months.
Aluminium/Aluminium blister: 24 months.
Tablet halves should be used within one day.

6.4. Special precautions for storage

Do not store above 25ºC.
Store in the original package.
Store tablet halves in the original blister in the original package

6.5 Nature and composition of immediate packaging

1 carton contains:
1, 2, 3, 4, 5, 6 or 7 PVC/PE/PVDC/Alu-foil blisters of 14 tablets each.
or
1,2,3,4,5,6,7 Alu/Alu-foil blisters of 14 tablets each.

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 product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Le Vet B.V.
Wilgenweg 7
3421 TV Oudewater
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Benazepril hydrochloride 5 mg tabletten voor honden
Benazepril hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCES

Benazepril hydrochloride 5 mg
Colourant: Iron oxides (E172) 0.5 mg

3. PHARMACEUTICAL FORM

Tablets

4. PACKAGE SIZE

14, 28, 42, 56, 70, 84 or 98 tablets

5. TARGET SPECIES

Dogs

6. INDICATION(S)

For treatment of congestive heart failure in dogs.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Not applicable

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC.

Store in the original package.
Tablet halves should be used within one day.
Store tablet halves in the original blister in the original package.

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

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

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

For animal treatment only.

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

Le Vet B.V.
Wilgenweg 7
3421 TV Oudewater
The Netherlands

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Benazepril hydrochloride 5 mg tabletten voor honden
Benazepril hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Le Vet B.V.

3. EXPIRY DATE

EXP{month/year}

4. BATCH NUMBER

Lot {number}

5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Benazepril hydrochloride 5 mg tabletten voor honden

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

Marketing authorisation holder:
Le Vet B.V.
Wilgenweg 7
3421 TV Oudewater
The Netherlands

Manufacturer responsible for batch release[1]:
Lelypharma B.V.
Zuiveringweg 42
8243 PZ Lelystad
The Netherlands

Genera Inc.
Svetonedeljska cesta 2, Kalinovica
10436 Rakov Potok
Croatia

[1]The printed package leaflet will state the name and address of the manufacturer responsible for the release of the concerned batch only.

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Benazepril hydrochloride 5 mg tabletten voor honden
Benazepril hydrochloride

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

Each tablet contains 5 mg benazepril hydrochloride
Colourant: Iron oxides (E172) 0.5 mg

Yellow, oblong divisible tablets, with a break mark on both sides.

4. INDICATION(S)

The product belongs to a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors. It is prescribed by the veterinary surgeon for the treatment of congestive heart failure in dogs.

5. CONTRAINDICATIONS

Do not use in case of hypersensitivity to the active substance benazepril hydrochloride or to any ingredient of the tablets.
Do not use in cases of hypotension (low blood pressure), hypovolemia (low blood volume), hyponatraemia (low blood sodium levels) or acute renal failure.
Do not use in cases of cardiac output failure due to aortic or pulmonary stenosis.
Do not use in pregnant or lactating dogs because the safety of benazepril hydrochloride has not been established during pregnancy or lactation in this species.

6. ADVERSE REACTIONS

Some dogs with congestive heart failure may exhibit vomiting or fatigue during treatment.
In dogs with chronic kidney disease there may be a moderate increase in levels of creatinine, an indicator of kidney function, in the blood. This is likely due to the effect of the medication in reducing the blood pressure within the kidney and is therefore not necessarily a reason for treatment to be stopped, unless the animal is showing other adverse reactions.

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.

Alternatively you can report via your national reporting system {national system details}.

7. TARGET SPECIES

Dogs

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

The product should be given orally once daily, with or without food. The duration of treatment is unlimited.

The product should be administered orally at a minimum dose of 0.25 mg (range 0.25-0.5) benazepril hydrochloride/kg body weight once daily, according to the following table:

Weight of dog (kg)	Benazepril hydrochloride 5 mg tabletten voor honden	
	Standard dose	Double dose
>5-10	0.5 tablet	1 tablet
>10-20	1 tablet	2 tablets

In dogs with congestive heart failure, the dose may be doubled, still administered once daily, to a minimum dose of 0.5 mg (range 0.5-1.0) benazepril hydrochloride/kg bodyweight if judged necessary and advised by the veterinary surgeon. Always follow the dosing instructions given by the veterinary surgeon.
In case of using halved tablets: Put the remaining half of a divided tablet back in the blister pocket and store it in a dry place below 25ºC. Use the remaining tablet half for the next administration.

9. ADVICE ON CORRECT ADMINISTRATION

For animal treatment only. For oral use only.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Do not store above 25ºC.
Store in the original package
Do not use after the expiry date stated on the carton after EXP.
Tablet halves should be used within one day.
Store tablet halves in the original blister in the original package.

12. SPECIAL WARNING(S)

Special warnings for each target species:
The efficacy and safety of the product has not been established in dogs below 2.5 kg body weight.

Special precautions for use in animals:
In cases of chronic kidney disease, your veterinarian will check the hydration status of your pet before starting therapy, and may recommend that regular blood tests are carried out during therapy in order to monitor plasma creatinine concentrations and blood erythrocyte counts.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Wash hands after use.
In case of accidental oral ingestion, seek medical advice immediately and show the label or the package leaflet to the physician.
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.

Pregnancy and lactation:
Do not use during pregnancy or lactation. The safety of the product has not been established in breeding, pregnant or lactating dogs.

Interaction with other medicinal products and other forms of interaction:
Inform the veterinary surgeon if the animal is taking, or has recently taken, any other medicines.
In dogs with congestive heart failure, benazepril hydrochloride has been given in combination with digoxin, diuretics, pimobendan and anti-arrhythmic products without evidence of associated adverse reactions.
In humans, the combination of ACE inhibitors and NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) can lead to reduced anti-hypertensive efficacy or impaired kidney function. The combination of the product and other anti-hypertensive agents (e.g. calcium channel blockers, β-blockers or diuretics), anaesthetics or sedatives may lead to additive hypotensive effects. Therefore, concurrent use of NSAIDs or other medications with a hypotensive effect should be considered with care.
Your veterinary surgeon may recommend to closely monitor kidney function and for signs of hypotension (lethargy, weakness etc) and treat these if necessary.
Interactions with potassium-preserving diuretics like spironolactone, triamterene or amiloride cannot be ruled out. Your veterinary surgeon may recommend to monitor plasma potassium concentrations when using the product in combination with a potassium-sparing diuretic because of the risk of hyperkalaemia (high blood potassium).

Overdose (symptoms, emergency procedures, antidotes):
Transient reversible hypotension (low blood pressure) may occur in cases of accidental overdose. Therapy should consist of intravenous infusion of warm isotonic saline.

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

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

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

Pharmacodynamic properties
Benazepril hydrochloride is a pro-drug hydrolysed in vivo to its active metabolite, benazeprilat.

Benazeprilat is a highly potent and selective inhibitor of the angiotensin converting enzyme (ACE), thus preventing the conversion of inactive angiotensin I to active angiotensin II and thereby also reducing synthesis of aldosterone. Therefore, it blocks effects mediated by angiotensin II and aldosterone, including vasoconstriction of both arteries and veins, retention of sodium and water by the kidney and remodelling effects (including pathological cardiac hypertrophy and degenerative renal changes).

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

Benazepril hydrochloride reduces the blood pressure and volume load on the heart in dogs with congestive heart failure.

In contrast with other ACE inhibitors, benazeprilat is excreted equally by both biliary and urinary routes in dogs, and therefore no adjustment of the dose of the product is necessary in the treatment of cases with renal insufficiency.

1 carton contains:
1, 2, 3, 4, 5, 6 or 7 PVC/PE/PVDC/Alu-foil blisters of 14 tablets each.
or
1,2,3,4,5,6,7 Alu/Alu-foil blisters of 14 tablets each.

Not all pack sizes may be marketed.