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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

BENADIL 5 mg, film-coated tablets for dogs and cats (BE, CZ, DE, HU, LU, NL, PL, PT, SK)
BENADIL 5, film-coated tablets for dogs and cats (FR)
KELAPRIL 5 mg, film-coated tablets for dogs and cats (UK)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Active substance:
Benazepril hydrochloride 5 mg
(equivalent to benazepril 4.6 mg)

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Lactose monohydrate	
Cellulose microcrystalline	
Starch pregelatinised	
Castor oil hydrogenated	
Crospovidone	
Silica colloidal anhydrous	
Coating: Macrogol poly(vinyl alcohol) grafted copolymer Poly(vinyl alcohol) Silica colloidal anhydrous Talc Macrogol 6000 Titanium dioxide (E171) Iron oxide yellow (E172)	 0.52 mg 0.06 mg

Light yellow, oval divisible film-coated tablets scored on both sides.

3. CLINICAL INFORMATION

3.1 Target species

Dogs, cats

3.2 Indications for use for each target species

Dogs:
Treatment of congestive heart failure.

Cats:
Reduction of proteinuria associated with chronic kidney disease.

3.3 Contraindications

Do not use in cases 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 in pregnancy or lactation (see section 3.7).

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:

No evidence of renal toxicity of the veterinary medicinal product has been observed (in dogs or cats) 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 veterinary medicinal product has not been established in dogs and cats 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.
To avoid accidental ingestion, particularly by a child, unused part-tablets should be returned to the open blister space and inserted back into the carton.
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.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Dogs:

Rare (1 to 10 animals / 10,000 animals treated):	Vomiting; Fatigue
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Elevated creatinine[1]; Incoordination

[1] 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.

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

Cats:

Rare (1 to 10 animals / 10,000 animals treated):	Diarrhoea, Emesis; Anorexia, Dehydration, Lethargy
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Elevated creatinine[1]; Increased appetite, Weight gain

[1] In cats 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.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:
Do not use during pregnancy or lactation.
The safety of the veterinary medicinal product has not been established in pregnant or lactating dogs and cats.
Embryotoxic effects (foetal urinary tract malformation) were seen in trials with laboratory animals (rats) at maternally non-toxic doses.

Fertility:
The safety of the veterinary medicinal product has not been established in breeding dogs and cats.
Benazepril reduced ovary/oviduct weights in cats when administered daily at 10 mg/kg body weight for 52 weeks.

3.8 Interaction with other medicinal products and other forms of interaction

In dogs with congestive heart failure, the veterinary medicinal product 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 anti-hypertensive efficacy or impaired renal function. The combination of the veterinary medicinal 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. 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 the veterinary medicinal product in combination with a potassium sparing diuretic because of the risk of hyperkalaemia.

3.9 Administration routes and dosage

Oral use.

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

Dogs:

The veterinary medicinal 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)	"Product name" 5 mg (to be completed nationally)	
	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.

Cats:

The veterinary medicinal product should be administered orally at a minimum dose of 0.5 mg (range 0.5-1.0) benazepril hydrochloride/kg body weight once daily according to the following table:

Weight of cat (kg)	"Product name" 5 mg (to be completed nationally)
2.5 - 5	0.5 tablet
> 5 - 10	1 tablet

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

The veterinary medicinal product reduced erythrocyte counts in normal cats when dosed at 10 mg/kg body weight once daily for 12 months and 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 cats or dogs.
Transient reversible hypotension may occur in cases of accidental overdose. Therapy should consist of intravenous infusion of warm isotonic saline.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QC09AA07

4.2 Pharmacodynamics

Benazepril hydrochloride is a prodrug 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 veterinary medicinal product causes long-lasting inhibition of plasma ACE activity in dogs and cats, with more than 95% inhibition at peak effect and significant activity (>80% in dogs and >90% in cats) persisting 24 hours after dosing.

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

In cats with experimental renal insufficiency, the veterinary medicinal product normalized the elevated glomerular capillary pressure and reduced the systemic blood pressure.

Reduction in glomerular hypertension may retard the progression of kidney disease by inhibition of further damage to the kidneys. Placebo controlled clinical field studies in cats with chronic kidney disease (CKD) have demonstrated that the veterinary medicinal product significantly reduced levels of urine protein and urine protein to creatinine ratio (UPC); this effect is probably mediated via reduced glomerular hypertension and beneficial effects on the glomerular basement membrane.
No effect of the veterinary medicinal product on survival in cats with CKD has been shown, but the veterinary medicinal product increased the appetite of the cats, particularly in more advanced cases.

4.3 Pharmacokinetics

After oral administration of benazepril hydrochloride, peak levels of benazepril are attained rapidly (T_{max} 0.58 hour in dogs and 0.43 hour in cats) and decline quickly as the drug is partially metabolised by liver enzymes to benazeprilat.
The systemic bioavailability is incomplete (~13% in dogs) due to incomplete absorption (38% in dogs and <30% in cats) and first pass metabolism.

In dogs, peak benazeprilat concentrations (C_{max} of 39.4 ng/ml after a dose of 0.40 mg/kg benazepril hydrochloride) are achieved with a T_{max} of 1.43h.
In cats, peak benazeprilat concentrations (C_{max} of 479.2 ng/ml after a dose of 0.95 mg/kg benazepril hydrochloride) are achieved with a T_{max} of 1.91h.

Benazeprilat concentrations decline biphasically: the initial fast phase ($t_{1/2}$=1.7 hours in dogs and $t_{1/2}$=2.4 hours in cats) represents elimination of free drug, while the terminal phase ($t_{1/2}$=19 hours in dogs and $t_{1/2}$=29 hours in cats) 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 the veterinary medicinal product leads to slight bioaccumulation of benazeprilat (R=1.47 in dogs and R=1.36 in cats 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 and 85% via the biliary and 15% via the urinary route in cats. The clearance of benazeprilat is not affected in dogs or

cats with impaired renal function and therefore no adjustment of the veterinary medicinal product dose is required in either species in cases of renal insufficiency.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life of divided tablets: 2 days.

5.3 Special precautions for storage

Store below 25°C in the original package.
Store in a dry place.
Each time an unused half tablet is stored, it should be returned to the open blister space inserted back into the cardboard box and used at the next administration.

5.4 Nature and composition of immediate packaging

PVC/PCTFE – aluminium blister or alu-foil (oPA/PVC) – aluminium blister containing 14 film-coated tablets.
Cardboard box with

- 2 blisters (28 tablets);
- 7 blisters (98 tablets).

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater of household waste.
Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

VetViva Richter GmbH

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation:

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).