SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT:

VETPRIL 5 mg film-coated tablet for dogs and cats

[ES, PT, UK]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each divisible tablet contains:

Benazepril .....4.6 mg

(equivalent to Benazepril Hydrochloride 5 mg)

Excipients :

Titanium dioxide (E171).....1.929 mg

Iron oxide yellow (E172) .....0.117 mg

Iron oxide red (E172).....0.014 mg

Iron oxide black (E172).....0.004 mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM:

Film-coated tablet

Beige oblong biconvex film-coated divisible tablets

4. CLINICAL PARTICULARS:

4.1 Target species:

Dogs and cats.

4.2 Indications for use, specifying target species:

In DOGS: weighing more than 5 kg bw: Treatment of congestive heart failure.
In CATS: Reduction of proteinuria associated with chronic kidney disease.

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.

See Section 4.7.

4.4 Special warnings for each target species

4.5 Special precautions for use

i. Special precautions for use in animals

No evidence of renal toxicity to benazepril 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 benazepril has not been established in dogs and cats below 2.5 kg body weight.

ii. 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 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 cats and dogs with chronic kidney disease, benazepril 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.

Benazepril may increase food consumption and body weight in cats.

Emesis, anorexia, dehydration, lethargy and diarrhoea have been reported in rare occasions in cats.

It is recommended to monitor plasma creatinine and erythrocyte counts during therapy.

4.7 Use during pregnancy and lactation

Do not use during pregnancy or lactation. The safety of benazepril has not been established in breeding, pregnant or lactating dogs and cats. Benazepril reduced ovary/oviduct weights in cats when administered daily at 10 mg/kg body weight for 52 weeks. Embryotoxic effects (foetal urinary tract malformation) were seen in trials with laboratory animals (rats) at maternally nontoxic doses.

4.8 Interaction with other medicaments and other forms of interaction:

In dogs with congestive heart failure, benazepril 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 benazepril and other anti-hypertensive agents (e.g.

calcium channel blockers, beta-adrenergic antagonists 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 in combination with a potassium sparing diuretic because of the risk of hyperkalaemia.

4.9 Amounts to be administered and administration route:

In dogs:

The dose is 0.23 mg benazepril /kg bw per day, corresponding to 0.25 mg of Benazepril hydrochloride / kg bw per day. It should be given orally once daily, with or without food. It corresponds to 1 tablet per 20 kg given according to the following regime:

Weight of dog (kg)	Number of tablets
5 - 10	0.5
11 - 20	1

The dose may be doubled, still administered once daily, if judged clinically necessary and advised by the veterinary surgeon.

In cats:

The dose is 0.46 mg benazepril /kg bw per day, corresponding to 0.50 mg of Benazepril hydrochloride / kg bw per day. It should be given orally once daily, with or without food. It corresponds to 1 tablet per 10 kg given according to the following regime:

Weight of cat (kg)	Number of tablets
2.5 – 5.0	0.5
5.1 – 10.0	1

4.10 Overdose (symptoms, emergency procedures, antidotes):

Benazepril 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.

4.11 Withdrawal period:

Not applicable

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: ACE inhibitors, benazepril
ATCvet code: QC09AA07

5.1 Pharmacodynamic properties

Benazepril hydrochloride is a prodrug hydrolysed in vivo to benazeprilat. This active metabolite inhibits angiotensin converting enzyme (ACE), thus preventing the conversion of inactive angiotensin I into 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 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.

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

In cats with experimental renal insufficiency, benazepril 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 benazepril 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 benazepril on survival in cats with CKD has been shown, but benazepril increased the appetite of the cats, particularly in more advanced cases.

5.2. Pharmacokinetic properties

After oral administration, benazepril is rapidly absorbed from the gastrointestinal tract. One part of absorbed benazepril is hydrolyzed by hepatic enzymes to the active substance, benazeprilat; unchanged benazepril and hydrophilic metabolites account for the remainder. The absolute systemic bioavailability, calculated for oral benazepril versus intravenous benazepril is about 9%. Peak benazeprilat concentrations are achieved within about 2 hours, both in fasting and fed situations.
Benazepril and benazeprilat are extensively bound to plasma proteins. Repeated administration leads to slight accumulation of benazeprilat in plasma, steady state being achieved in less than 4 days.
In dogs, the major part of benazeprilat is rapidly eliminated, and it is excreted equally via hepatic and urinary routes.
After the administration of a single dose of the product (0.23 mg benazepril/ kg b.w.), peak benazeprilat concentrations (Cmax of 40.9 ng/ml) were achieved within about 1.5 h (Tmax of 1.5h), with AUC of 320.5 ng/ml.h and a half-life ($t_{1/2}$) of 12.4 h.
In cats, benazeprilat is excreted 85% via the biliary and 15% via the urinary route. The clearance of benazeprilat is not affected in cats with decreased glomerular filtration; therefore, no adjustment of the dose is required.
After the administration of a single dose of the product in cats (0.46 mg benazepril/ kg b.w.), peak benazeprilat concentrations (Cmax of 198.7 ng/ml) were achieved within about 1.0 h (Tmax of 1.03h), with AUC of 969.4 ng/ml.h and a half-life ($t_{1/2}$) of 13.9 h.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Iron oxide yellow (E-172)
Iron oxide red (E-172)
Iron oxide black (E-172)
Titanium dioxide (E-171)
Cellulose microcrystalline
Lactose monohydrate
Povidone
Maize starch
Silica colloidal anhydrous
Magnesium stearate
Hypromellose
Macrogol 8000

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

Shelf life of the veterinary medicinal product as packaged for sale: 18 months
Return any halved tablet to the blister pack and use within 1 day. The blister pack should be inserted back into the cardboard box.

6.4 Special precautions for storage:

Do not store above 25°C.
Protect from light. Store in a dry place.

6.5 Nature and composition of immediate packaging:

Blister made of clear film of PVC/PE/PVDC and aluminium film containing 14 tablets.
Box with:
- 1 blister (14 tablets)
- 10 blisters (140 tablets)

Not all pack size 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

Vetpharma animal Health, S.L.
Les Corts, 23
08028 Barcelona
SPAIN

8. MARKETING AUTHORISATION NUMBERS

Vm 32509/4010

9. DATE OF THE FIRST AUTHORISATION

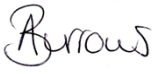
28 January 2013

10. DATE OF REVISION OF THE TEXT

January 2013

PROHIBITION OF SALE, SUPPLY AND/OR USE

Under veterinary prescription

Approved:  **28/01/2013**