

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

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.

Wash hands after use.

In case of accidental ingestion by children, seek medical advice immediately and show this label or the package leaflet to the doctor.

iii) Other precautions

None

4.6 Adverse reactions (frequency and seriousness)

At the start of the treatment, a decrease of the blood pressure and a transient increase of plasmatic concentrations of creatinine may occur.

On rare occasions, transient signs of hypotension, such as lethargy and ataxia may occur.

4.7 Use during pregnancy, lactation or lay

Studies in laboratory animals (rats) have shown embryotoxic effects (malformations of the foetal urinary system) at doses not toxic for the mother.

The safety of the medicinal product has not been studied in pregnant or lactating females.

Do not use during pregnancy or lactation.

Do not use in breeders.

4.8 Interaction with other medicinal products and other forms of interaction

None known in dogs.

In dogs with heart failure, benazepril has been given in combination with digoxin, diuretics and anti-arrhythmic drugs without demonstrable adverse interactions.

Interactions with potassium sparing diuretics, like spironolactone, triamteren and amiloride, can not be excluded.

The concurrent administration of potassium-sparing diuretics should only be considered under regular monitoring of plasma potassium.

The association of this product with other anti-hypertensive agents (e.g.: calcium channel blockers, β -blockers or diuretics), anaesthetics or sedatives may lead to additive hypotensive effect.

In humans, the association of ACE inhibitors and NSAIDs can lead to reduced anti-hypertensive efficacy or impaired renal function. Therefore concurrent administration with NSAIDs or other medications with hypotensive effect should be considered with care.

The concomitant administration of NSAIDs or ciclosporin requires a survey of the renal function.

4.9 Amounts to be administered and administration route

Oral administration

0.23 mg of benazepril per kg bodyweight per day, equivalent to 0.25 mg of benazepril hydrochloride per kg bodyweight per day, as one administration, with or without a meal, i.e one tablet per 20 kg as shown in the following table:

Dog weight (kg)	Number of tablets
2.5 - 5	0.25
5 - 10	0.50
10 - 15	0.75
15 - 20	1

In case of use of quarters or half tablets: Put the remaining quantity of the tablet back into the blister pocket and use for the next administration.

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

The tablets are flavoured and may be taken spontaneously by dogs, but can also be administered directly into the dog's mouth or be given with food if necessary.

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

Transient and reversible signs of hypotension may appear in case of accidental overdose. Treatment is symptomatic, involving intravenous infusion with warm isotonic saline.

Morphologic changes such as hypertrophy or hyperplasia of juxtaglomerular cells, increase of uremia and a weight loss of the heart due to an involution have been observed with doses over 10 mg/kg in healthy dogs.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Cardiovascular system, ACE Inhibitor, Benazepril.
ATCvet code: QC09AA07

5.1 Pharmacodynamic properties

Benazepril hydrochloride is a prodrug hydrolysed in vivo to benazeprilat which inhibits angiotensin converting enzyme (ACE), thus preventing the conversion of inactive angiotensin I into active angiotensin II. Therefore, benazeprilat inhibits all effects mediated by angiotensin II, including vasoconstriction of both arteries and veins and retention of sodium and water by the kidney. Benazeprilat causes long-lasting inhibition of plasma ACE, with significant inhibition persisting for 24 hours after a single dose.

In dogs with heart failure, benazepril reduces the peripheral resistance, blood pressure of left ventricle and volume load on the heart.

5.2 Pharmacokinetic particulars

Following oral administration, benazepril is rapidly absorbed from the gastrointestinal tract. Absorbed benazepril is partly 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 5-8 %, because of incomplete absorption and first pass metabolism.. After oral administration of 0.5 mg/kg of benazepril hydrochloride, peak benazeprilat plasmatic concentrations (C_{max} approximately $30 \text{ ng}\cdot\text{mL}^{-1}$) are achieved within about 1 and half hours. The plasmatic concentrations (AUC_{tot}) area under the curve is close to $193 \text{ ng}\cdot\text{h}\cdot\text{mL}^{-1}$

Benazepril and benazeprilat are both extensively bound to plasma proteins and in tissue it mainly resides in kidney and liver. There is no significant difference in the pharmacokinetics, whether benazepril hydrochloride is administered to fed or fasted dogs.

The elimination half-life of benazeprilate is approximately 13 hours.

Repeated administration leads to slight accumulation, steady state being achieved in less than 4 days.

In dogs, benazepril is equally excreted by hepatic or urinary route.

The clearance of benazepril is not appreciably affected in dogs with impaired renal or hepatic functions and therefore no adjustment of the dose is required in cases of renal insufficiency.

5.3 Environmental properties

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pig liver flavour

Yeast

Lactose monohydrate

Croscarmellose sodium

Anhydrous colloidal silica

Hydrogenated castor oil

Microcrystalline cellulose

6.2 Incompatibilities

None known

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 21 months.

Shelf-life of divisions of the tablets: 72 hours

6.4. Special precautions for storage

Do not store above $30 \text{ }^{\circ}\text{C}$

Store in original package in order to protect from moisture.

Any part-used tablet should be returned to the opened blister and used within 3 days

6.5 Nature and composition of immediate packaging

[PA-Al-PVC] / Aluminium heat sealed blister strip of 10 tablets

Cardboard box with 1 blister strip of 10 tablets
Cardboard box with 5 blister strips of 10 tablets
Cardboard box with 10 blister strips of 10 tablets
Cardboard box with 25 blister strips of 10 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

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8. MARKETING AUTHORISATION NUMBER

Vm 20749/4015

9. DATE OF FIRST AUTHORISATION

7 September 2009

10 DATE OF REVISION OF THE TEXT

7 September 2009

PROHIBITION OF SALE, SUPPLY AND/OR USE

To be completed in accordance with national requirements.