ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nelio 2.5 mg tablet for cats

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substance:
Benazepril (as hydrochloride)..... 2.30 mg
(equivalent to benazepril hydrochloride..... 2.50 mg)

Excipients:

Qualitative composition of excipients and other constituents
Pig liver flavour
Yeast
Lactose monohydrate
Croscarmellose sodium
Anhydrous colloidal silica
Hydrogenated castor oil
Microcrystalline cellulose

Oblong shaped scored beige tablet, divisible into halves.

3. CLINICAL INFORMATION

3.1 Target species

Cats.

3.2 Indications for use for each target species

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 during pregnancy or lactation (section 3.7).

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:
Efficacy and safety of benazepril have not been established in cats of weight less than 2.5 kg

No evidence of renal toxicity to the veterinary medicinal product has been observed in 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.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Angiotensin converting enzyme (ACE) inhibitors have been found to affect the unborn child during pregnancy in humans. Pregnant women should take special care to avoid accidental oral exposure. Wash hands after use.
In case of accidental oral ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Special precautions for the protection of the environment:
Not applicable.

3.6 Adverse events

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]
Undetermined frequency (cannot be estimated from the available data):	Increased appetite, Weight gain

[1]At the start of therapy, in cats with chronic kidney disease. 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 therefore is 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:
The safety of the veterinary medicinal product has not been established in breeding, pregnant or lactating cats Benazepril reduced ovary / oviduct weights in cats when administered daily at 10 mg / kg for 52 weeks. Embryotoxic effects (foetal urinary tract malformation) were seen in trials with laboratory animals (rats) at maternally nontoxic doses.
Do not use during pregnancy or lactation.

3.8 Interaction with other medicinal products and other forms of interaction

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, beta-

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.
The veterinary medicinal product tablets are flavoured and are taken voluntarily by most cats.

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:

Cat weight (kg)	Number of tablets
2.5 – 5	1
>5 – 10	2

To ensure a correct dosage, body weight should be determined as accurately as possible.

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

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 but this effect was not observed at the recommended dose during clinical trials in cats.
Transient reversible hypotension may occur in cases of accidental overdose. Therapy should consist of intravenous infusion with 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 cats, with more than 95% inhibition at peak effect and significant activity (>90% in cats) persisting 24 hours after dosing.
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 (Tmax 2 hours in cats) and decline quickly as the active substance is partially metabolised by liver enzymes to benazeprilat. The systemic bioavailability is incomplete due to incomplete absorption (<30% in cats) and first pass metabolism.
In cats, peak benazeprilat concentrations (Cmax of 110.0 ng/ml after a dose of 0.65 mg/kg benazepril hydrochloride) are achieved with a Tmax of 1 hour and half.
Benazeprilat concentrations decline biphasically: the initial fast phase (t1/2=2.4 hours in cats) represents elimination of free drug, while the terminal phase (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.
Repeated administration of the veterinary medicinalproduct leads to slight bioaccumulation of benazeprilat (R=1.36 in cats with 0.5 mg/kg), steady state being achieved within a few days.
Benazeprilat is excreted 85% via the biliary and 15% via the urinary route in cats. The clearance of benazeprilat is not affected in cats with impaired renal function and therefore no adjustment of the veterinary medicinal product dose is required in cases of renal insufficiency.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

None known.

5.2 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf-life of divisions of the tablets*:* 24 hours.

5.3 Special precautions for storage

Do not store above 25°C.
Store in original package.
Any part-used tablet should be returned to the opened blister and used within 24 hours.

5.4 Nature and composition of immediate packaging

Polyamide-Aluminium-Polyvinylchloride/Aluminium heat-sealed blister strip of 10 tablets
or
Poylamide-Aluminium-Desicant/Aluminium heat-sealed blister pack 10 tablets per strip.

Box with 1 strip of 10 tablets
Box with 2 strips of 10 tablets
Box with 5 strips of 10 tablets
Box with 10 strips of 10 tablets
Box with 14 strips of 10 tablets
Box with 18 strips of 10 tablets

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater or 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

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: {DD/MM/YYYY}

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

{mm/yyyy}

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).

ANNEX III

LABELLING AND PACKAGE LEAFLET

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nelio 2.5 mg tablet

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains:
Active substance :
Benazepril (as hydrochloride)..... 2.30 mg
(equivalent to benazepril hydrochloride..... 2.50 mg)

3. PACKAGE SIZE

10 tablets
20 tablets
50 tablets
100 tablets
140 tablets
180 tablets

4. TARGET SPECIES

Cats.

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Oral use.

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp.{mm/yyyy}
Shelf-life of divisions of the tablets*:* 24 hours.

9. SPECIAL STORAGE PRECAUTIONS

Do not store above 25 °C

Store in original package.
Any part-used tablet should be returned to the opened blister and used within 24 hours

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

11. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only

12. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Blister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nelio

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

2.5 mg of benazepril hydrochloride

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Nelio 2.5 mg tablet for cats

2. Composition

Each tablet contains:
Active substance:
Benazepril (as hydrochloride)..... 2.30 mg
(equivalent to benazepril hydrochloride..... 2.50 mg)

Oblong shaped scored beige tablet, divisible into halves.

3. Target species

Cats.

4. Indications for use

Reduction of proteinuria associated with chronic kidney disease.

5. 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 (low blood pressure), hypovolemia (low blood volume) 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 : Special warnings).

6. Special warnings

Special precautions for safe use in the target species:
Efficacy and safety of benazepril have not been established in cats of weight less than 2.5 kg
No evidence of renal toxicity to the veterinary medicinal product has been observed in 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.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Angiotensin converting enzyme (ACE) inhibitors have been found to affect the unborn child during pregnancy in humans. Pregnant women should take special care to avoid accidental oral exposure.
Wash hands after use.
In case of accidental oral ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established in breeding, pregnant or lactating cats Benazepril reduced ovary / oviduct weights in cats when administered daily at 10 mg /

kg for 52 weeks. Embryotoxic effects (foetal urinary tract malformation) were seen in trials with laboratory animals (rats) at maternally nontoxic doses.
Do not use during pregnancy or lactation.

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 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 veterinary medicinal product and other anti-hypertensive agents (e.g. calcium channel blockers, beta-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 veterinary medicinal product in combination with a potassium-sparing diuretic because of the risk of hyperkalaemia (high blood potassium).

Overdose:
Transient reversible hypotension (low blood pressure) may occurs in case of accidental overdose. Therapy should consist of intravenous infusion of warm isotonic saline.

Major incompatibilities:
None known.

7. Adverse events

Cats:

Rare (1 to 10 animals / 10,000 animals treated):
Diarrhoea, Emesis (vomiting), Anorexia, Dehydration, Lethargy
Very rare (<1 animal / 10,000 animals treated, including isolated reports):
Elevated creatinine[1]
Undetermined frequency (cannot be estimated from the available data):
Increased appetite, Weight gain

[1]At the start of therapy, in cats with chronic kidney disease. 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 therefore is 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. 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 contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder or its local representative of the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system.

8. Dosage for each species, routes and method of administration

Oral use.

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

In 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:

Cat weight (kg)	Number of tablets
2.5 – 5	1
>5. – 10	2

9. Advice on correct administration

To ensure a correct dosage, body weight should be determined as accurately as possible.
The veterinary medicinal product tablets are flavoured and are taken voluntarily by most cats.
In case of use of half tablets: Put the remaining half of the tablet back into the blister pocket and use for the next administration.

10. Withdrawal periods

Not applicable.

11. Special storage precautions

Keep out of the sight and reach of children.
Do not store above 25 C
Store in original package.
Shelf-life of divisions of the tablets: 24 hours.
Any part-used tablet should be returned to the opened blister and used within 24 hours.
Do not use this veterinary medicinal product after the expiry date which is stated on the blister and outer carton after Exp. The expiry date refers to the last day of that month.

12. Special precautions for disposal

Medicines should not be disposed of via wastewater or 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 applicable national collection systems. These measures should help to protect the environment.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorization numbers and pack sizes

(MA)

Pack sizes:
Box with 1 strip of 10 tablets
Box with 2 strips of 10 tablets
Box with 5 strips of 10 tablets
Box with 10 strips of 10 tablets
Box with 14 strips of 10 tablets
Box with 18 strips of 10 tablets

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

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

16. Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:
(Name and address to be completed nationally)
Tel: +800 35 22 11 51
Email: pharmacovigilance@ceva.com

Manufacturer responsible for batch release:
Ceva Santé Animale
Boulevard de la Communication
Zone Autoroutière
53950 Louverné
FRANCE

17. Other information

Pharmacodynamics
Benazepril hydrochloride is a prodrug 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).The veterinary medicinal product causes long-lasting inhibition of plasma ACE activity in cats, with more than 95% inhibition at peak effect and significant activity (>90% in cats) persisting 24 hours after dosing.
y and degenerative renal changes).The veterinary medicinal product causes long-lasting inhibition of plasma ACE activity in cats, with more than 95% inhibition at peak effect and significant activity (>90% in cats) persisting 24 hours after dosing.
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.
In a clinical trial in cats with chronic kidney disease, the veterinary medicinal product significantly reduced protein loss in the urine; this effect is probably mediated via reduced glomerular hypertension

and beneficial effects on the glomerular basement membrane. The veterinary medicinal product also increased the appetite of the cats, particularly in more advanced cases.
In contrast with other ACE inhibitors, benazeprilat is excreted 85% via the biliary and 15% via the urinary route in cats, and therefore no adjustment of the dose of the veterinary medicinal product is necessary in the treatment of cases with renal insufficiency.