AGENCE NATIONALE DU

MEDICAMENT VETERINAIRE

FRENCH AGENCY FOR FOOD, ENVIRONNEMENTAL AND OCCUPATIONAL HEALTH SAFETY

FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS

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PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

BENAMIX 6.25 mg/g premix for medicated feeding stuff for cats

PRODUCT SUMMARY

EU procedure number	FR/V/0497/001/DC
Name, strength and pharmaceutical form	BENAMIX 6.25 mg/g premix for medicated feeding stuff for cats
Applicant	VIRBAC 1ere avenue 2065 M L I D 06516 Carros cedex FRANCE
Active substance(s)	Benazepril hydrochloride
ATC vetcode	QC09AA07
Target species	Cats
Indication for use	Reduction of proteinuria associated with chronic kidney disease.

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VIRBAC	DCP
Publicly available assessment report	

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application	Bibliographic application in accordance with Article 22 of Regulation (EC) 2019/6, as amended.

1. SCIENTIFIC OVERVIEW

The veterinary medicinal product (VMP) is produced and controlled using validated methods and tests, which ensure the consistency of the VMP released on the market.

It has been shown that the VMP can be safely used in the target species; the reactions observed are indicated in the SPC.

The VMP is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.

The efficacy of the VMP was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

A. Product description

The VMP contains 5.76 mg/g of benazepril (as hydrochloride) and the excipients silica colloidal anhydrous, polysorbate 80, butylhydroxyanisole and medium chain triglycerides.

The container/closure system is an HDPE barrel closed by a PP screw cap.

The choice of the excipients and formulation are justified.

The VMP is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Description of the manufacturing method

The VMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

Process validation data on the VMP have been presented in accordance with the relevant European guidelines.

C. Production and control of starting materials

The active substance is benazepril hydrochloride, an established active substance described in the European Pharmacopeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control tests carried out on isolated intermediates during the manufacturing process

Not applicable.

E. Control tests on the finished product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification and their limits have been justified and are considered appropriate to adequately control the quality of the VMP.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F. Stability tests

A re-test period is set in the Certificates of Suitability of the active substance.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the VMP throughout its shelf life when stored under the approved conditions.

The shelf life after incorporation into feed (kibbles) is supported by the data provided.

3. SAFETY DOCUMENTATION (safety and residues tests)

This application is submitted in accordance with Article 22- Bibliographic application of Regulation (EU) 2019/6.

A. Safety tests

Pharmacological studies

See part IV.

Toxicological studies

The applicant has provided relevant bibliographical data to document the toxicological profile of benazepril. The lowest oral NOAEL for toxicity is 15 mg/kg body weight (from 26-week toxicity study in rats and 26-52-week toxicity study in dogs).
Benazepril showed embryotoxic/foetotoxic properties (as all angiotensin converting enzyme inhibitors (ACEIs)), but appears to be non-genotoxic and non-carcinogenic.

Other studies

Three additional well-conducted studies (in accordance with OCDE guidelines) were performed on the final formulation to assess skin sensitization, skin irritation and ocular irritation.
The veterinary medicinal product showed no potential for skin sensitization, no skin irritation and no eyes irritation.

Observations in humans

Benazepril is used as human medicine for several decades.

Indications are arterial hypertension and slowing the progress of renal insufficiency in patients with a glomerular nephropathy with hypertension and proteinuria.

The recommended dose for adults is 10 mg once a day. This posology should be reduced in patients over 70 years age.

For children (7-16 years), the recommended dose is 0.2 mg/kg (for a maximum of 10 mg/day), once daily. The posology should be updated in accordance with clinical response.
The most common adverse effects at recommended doses are: gastro-intestinal disturbances (nausea, diarrhoea, vomiting, abdominal pain), cutaneous signs (rash, pruritus, hypersensitivity reaction, pollakiuria, cough, symptoms of infection of high respiratory tract.
Medicinal products with benazepril are contraindicated in pregnant women during the 2nd and 3rd trimesters of pregnancy, unless if the treatment is considered crucial.

User safety

The applicant has provided a user safety assessment in compliance with the relevant guidelines.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guidelines which showed that no further assessment is required.
Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

A. Pre-Clinical Studies

Pharmacology

Pharmacodynamics (PD):

The applicant has provided bibliographical data to describe the mode of action of benazepril. The wording of mode of action in the proposed SPC corresponds to the wording of the product Fortekor.2.5 mg for cats.

Pharmacokinetics (PK):

The applicant has provided two comparative pharmacokinetic studies after repeat administration of Fortekor 2.5 mg tablet and the candidate medicated feed in healthy cats at 0.5-1mg/kg of benazepril per day for 8 days. Data show that pharmacokinetic profiles observed after repeated administrations of Fortekor tablets are more peaked with a lower baseline than the pharmacokinetic profile after repeated medicated feed administrations. Bioequivalence based on plasmatic benazeprilat concentrations is not demonstrated.

Angiotensin converting enzyme (ACE) inhibition (clinical endpoint) is at least similar after administration of the medicated feed than after Fortekor tablet.

In addition, sparse blood samples were collected at steady state during a clinical trial performed in CKD cats for the population PK/PD analysis (see clinical part).

Dose determination and confirmation

Bibliographical data show the well-established use of the minimum effective daily dose of 0.5 mg benazepril hydrochloride per kg bodyweight for the reduction of proteinuria associated with CKD in cats.

No dose determination study was conducted with the candidate product. A dose confirmation study was conducted on cats receiving the candidate product or Fortekor® to assess the effects of benazepril on ACE activity and to confirm the effect of the selected dose.

Tolerance in the target species of animals

The applicant has provided many bibliographic references to document the tolerance profile of benazepril in healthy cats, CKD and cardiac diseased cats.
Furthermore, the tolerance of the test product was also studied in the clinical trial.

The product literature accurately reflects the type and incidence of adverse effects, which might be expected.

B. Clinical trials

Bibliographic data was provided to prove the well-established use of benazepril for the intended indication (reduction of proteinuria associated with chronic kidney disease in cats) at the minimum daily effective dose of 0.5 mg benazepril HCl per kg bw. This scientific literature is related to Fortekor which was the first approved veterinary medicinal product for the proposed indication in cats. A population pharmacokinetic-pharmacodynamic analysis was provided with the aim to bridge the bibliographic data supporting the use of benazepril for the reduction of proteinuria in CKD cats.

PK and PD data were collected in cats with chronic kidney disease followed-up during a clinical trial and in healthy cats during pharmacokinetic studies.

The candidate product showed no statistically significant difference to Fortekor in the population pharmacokinetic-pharmacodynamic analysis using the concentrations of serum Angiotensin converting enzyme (ACE).

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the VMP for humans and the environment is acceptable.