Veterinary Medicines Directorate

**United Kingdom**
**Veterinary Medicines Directorate**
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**NATIONAL PROCEDURE**

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

## Benamix 6.25 mg/g Premix for Medicated Feeding Stuff for Cats

**Date Created: April 2025**

# MODULE 1

## PRODUCT SUMMARY

| | |
|---|---|
| Name, strength and pharmaceutical form | Benamix 6.25 mg/g Premix for Medicated Feeding Stuff for Cats, Premix for Medicated Feeding Stuff |
| Applicant | VIRBAC<br>1ère avenue 2065m LID<br>06516 Carros, France |
| Active substance | Benazepril Hydrochloride |
| ATC Vetcode | QC09AA07 |
| Target species | Cats |
| Indication for use | Reduction of proteinuria associated with chronic kidney disease (CKD). |

# MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

# MODULE 3

## PUBLIC ASSESSMENT REPORT

| | |
|---|---|
| Legal basis of original application | Full application in accordance with Article 8 of VMRs 2013 (Schedule 1, Para 7) as amended. |
| Date of conclusion of the procedure | 24/04/2025 |

## I. SCIENTIFIC OVERVIEW

This is a full bibliographic application, in accordance with Article 8 of VMRs 2013 (Schedule 1, Para 7) as amended, for approval in Great Britain (GB).

Benamix 6.25 mg/g Premix for Medicated Feeding Stuff for Cats contains 6.25 mg benazepril hydrochloride per gram. The product is indicated for the reduction of proteinuria associated with chronic kidney disease in cats. The product is to be administered orally, after incorporation into feed (kibble), to achieve a minimum dose of 0.5 mg benazepril hydrochloride/kg bodyweight per day, for the lifetime of the treated animal.

The distribution category of the product in GB is POM-V, a veterinary medicinal product subject to prescription.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC[1]. The product is safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy[2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

## II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

### *II.A. Composition*

The product contains benazepril hydrochloride and the excipients butylhydroxyanisole (E320), colloidal anhydrous silica, polysorbate 80 and medium chain triglycerides.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

The container/closure system consists of a plastic barrel (high density polyethylene) closed by a plastic screw cap (polypropylene cap equipped with an inviolability ring and a polyethylene seal). The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified.

The product is an established pharmaceutical form, and its development is adequately described in accordance with the relevant regulatory guidelines.

### *II.B. Description of the Manufacturing Method*

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of the dissolution or dispersion of the ingredients, followed by a filling step.

Process validation data on the product have been presented in accordance with the relevant regulatory guidelines.

### *II.C. Control of Starting Materials*

The active substance is benazepril hydrochloride, an established active substance described in the European Pharmacopoeia, supplied with a Certification of Suitability (CEP). 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.

The excipients all appear in the European Pharmacopoeia and their quality is compliant with Ph. Eur. standards.

The packaging materials are suitably controlled by the proposed specifications and satisfactory compliance statements were provided by the applicant.

### *II.C.4. Substances of Biological Origin*

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

### *II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process*

Not applicable.

### *II.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 product. 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. Control tests on the finished product are those appropriate for this pharmaceutical form.

### *II.F. Stability*

Stability data on the active substance have been provided in accordance with applicable regulatory guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

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

### *G. Other Information*

The shelf life of the veterinary medicinal product as packaged for sale is 2 years. The product should be used immediately after first opening the immediate packaging. The shelf life of the medicated feed is 12 months.

The product does not require any special storage conditions.

## III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

Due to the legal basis of the application, bibliographical data was supplied regarding pharmacological and toxicological information.

### *III.A Safety Documentation*

### *Pharmacological Studies*

Bibliographical data has been provided which describe the well-established mode of action of benazepril.

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 applicant has also provided bibliographical data which show the pharmacokinetics of benazepril.

Following oral administration, the lipophilic benazepril molecule is absorbed by the digestive tract. In humans, at least 37% of benazepril is absorbed after oral administration to fasted volunteers; $C_{max}$ of benazepril was achieved within 30 minutes. The rate of absorption of benazepril is slightly decreased when administered with food. After absorption, benazepril is rapidly metabolised in the liver into its active metabolite, benazeprilat, within 4 hours in humans.

Benazeprilat is not distributed extensively; in rats, the highest levels were detected in the lung and kidney, with very low levels in the brain. Passage through the blood-brain barrier and the placenta is minimal in rats, dogs, baboons, and humans. After administration of benazepril to lactating women, small amounts of benazepril and benazeprilat were secreted in milk, with an AUC in milk of around 1% of the corresponding value in plasma.

Only small amounts of benazepril (<1% of the dose) are excreted unchanged in the urine, whereas approximately 18% of the dose is recovered in the urine as benazeprilat. In humans, after 6 to 28 days of once daily administration of benazepril, no accumulation of benazepril and only slight accumulation of benazeprilat was observed.

### *Toxicological Studies*

The acute oral toxicity of benazepril has been reported to be very low in all species tested (rat, mouse, dog). The toxicity profile of benazepril via oral administration has been assessed in rodent and non-rodent species, in sub-chronic and chronic repeat-dose studies. After repeated administrations, benazepril induced thickening of the afferent glomerular arterioles due to the hypertrophy of the juxtaglomerular cells. The principal target organs for toxicity were kidney, heart, and liver. The observed effects after chronic administration of high doses were in most cases reversible and were related to the mode of action and pharmacology of ACE inhibitors.

Fertility and foetal development studies have been conducted in rats, mice, and rabbits. In all studies, maternal toxicity signs were reported at high doses. It was concluded that fertility and general reproductive performance were not impaired in these species, although the female mother rabbits were particularly sensitive to the hypotensive effects. ACE inhibitors generally do not impair fertility in animal studies. Despite benazepril demonstrating little or no teratogenicity in laboratory animal studies, it is known that perinatal use of ACE inhibitors has been demonstrated to cause foetal and neonatal morbidity, and death, in humans.

Studies have shown that benazepril has no known mutagenic or genotoxic effects. No evidence of carcinogenicity was observed in either mice or rats after

administration of benazepril in feed for up to 2 years. No evidence of immunotoxicity or neurotoxicity was shown in any studies.

Local tolerance has been evaluated in three GLP approved studies, performed on the final formulation of the premix and show good local tolerance regarding skin and eye irritation, and skin sensitisation.

### *User Safety*

A user risk assessment was provided in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following applicant's user recommendations are appropriate:

- The medicated feed may be harmful when ingested by children.
- Avoid accidental ingestion. The medicated feed and the feed bowl should be placed out of the reach and sight of children. In case of accidental oral ingestion, seek medical advice immediately and show the label of the medicated feed to the physician.
- Angiotensin converting enzyme (ACE) inhibitors have shown to affect the foetus. Pregnant women, and women of childbearing potential, should take special care to avoid any skin exposure with the medicated feed, including oral exposure due to hand-to-mouth contact.
- In case of accidental skin exposure or accidental ingestion, wash or rinse thoroughly and immediately with water, seek medical advice and show the label of the medicated feed to the physician.
- Angiotensin converting enzyme (ACE) may cause hypersensitivity reactions. People with known hypersensitivity to benazepril should avoid contact. In case of hypersensitivity reactions, seek medical advice and show the label of the medicated feed to the physician.
- Wash hands after use.

### *Environmental Safety*

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

**Phase I:**
The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

## IV. CLINICAL DOCUMENTATION

Due to the legal basis of this application, the applicant submitted bibliographic pharmacological and toxicological data for the active substance. Additionally, two pharmacokinetic studies and one field trial were conducted by the applicant to provide further pre-clinical and clinical evidence.

### *IV.I. Pre-Clinical Studies*

### *Pharmacology*

The applicant provided bibliographical information describing the pharmacodynamic and pharmacokinetic properties of the active substance.

The applicant also provided data from three studies to demonstrate the pharmacokinetics of the product compared to a tablet reference product of the same active ingredient. These included two pharmacokinetic studies and one field trial. Tests concluded that the test product is at least as effective as the reference product in inhibiting ACE.

### *Tolerance in the Target Species*

The applicant provided bibliographic references to support the tolerance profile of benazepril, when administered to both healthy cats and cats with CKD. One study reported an increase of serum creatinine following the administration of benazepril, which is a well-documented effect of this active substance.

The applicant also provided data from a clinical field study, conducted in four European member states. In this study, 112 cats received either the final formulation of the test product or a control product, which was a product containing the same active substance in tablet form. Adverse events were noted at a similar frequency between both groups and the conclusion was that the test product was considered safe for the treatment of cats with CKD.

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

## *IV.II. Clinical Documentation*

Bibliographic data was provided by the applicant to support the well-established use of benazepril hydrochloride for the treatment of proteinuria, associated with chronic kidney disease in cats, at the minimum daily effective dose of 0.5 mg benazepril hydrochloride per kg bodyweight. In these published studies, benazepril was well tolerated by the target species, and animals that received it presented a significant decrease of their urine protein:creatinine (UPC) ratios, compared to placebo populations.

### *Dose confirmation studies*

The applicant provided published literature to justify the well-established use of the minimum effective daily dose of 0.5 mg benazepril hydrochloride per kg bodyweight daily, with a dose range of 0.5 to 1 mg benazepril hydrochloride per kg bodyweight, for the product indication. No new dose determination studies were conducted with the product. However, pharmacological studies and a field study were presented in relation to dose confirmation.
In two pharmacokinetic studies, provided by the applicant, the product was tested against a reference product containing the same active ingredient in tablet

form. Results suggest that the candidate product would be more efficacious at ACE inhibition than the reference product because of the slower absorption rate of benazepril. Additionally, speed of consumption of the test product did not alter the pharmacokinetic profile of the benazeprilat plasma concentration.

Furthermore, the influence of quantity of the candidate product was evaluated by analysing data from the field study, where the product was tested against a reference product containing the same active ingredient in tablet form. This concluded that there is scope to have variation in feed intake throughout the day and between days, without negatively impacting the efficacy of ACE inhibition for the product.

### *Field Trials*

The applicant conducted a multicentric, randomised, blinded, positively controlled, GCP-compliant clinical field study, using the final formulation of the product. 112 cats were included in the study and allocated to either receive the test product or a control product (benazepril in a tablet format), for six months. Regarding the reduction in proteinuria, based on levels of ACE inhibition, non-inferiority of the test product compared to the control was concluded. This was also supported by the clinical efficacy parameters that evolved similarly in both groups during the study.

## V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that, when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the product is favourable.

# MODULE 4

## POST- AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)