IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Fortekor Flavour 5 mg Tablets for cats and dogs

PRODUCT SUMMARY

EU Procedure Number	IE/V/0430/001
Name, Strength, Pharmaceutical Form	Fortekor Flavour 5 mg Tablets for cats and dogs
Active Substances(s)	Benazepril hydrochloride
Applicant	Elanco GmbH Heinz-Lohmann-Strasse 4 27472 Cuxhaven Germany
Legal Basis of Application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended
Target Species	Cats,Dogs
Indication For Use	Treatment of congestive heart failure in dogs
ATC Code	QC09AA07
Date of completion of the original decentralised procedure	22 December 2009
Concerned Member States for original procedure	Austria, Czech Republic, Cyprus, Hungary, Ireland, Poland, Romania, Slovakia, Slovenia. Added via RMS change: UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

Fortekor Flavour5 mg Tablets for Dogs and Fortekor Flavour20 mg Tablets for Dogs are beige, ovaloid, divisible tablets intended to treat congestive heart failure in dogs. The tablets are given orally once daily, and are taken voluntarily, with or without food. The recommended dose for the products is 0.25-0.5 mg benazepril hydrochloride/kg bodyweight/day. The dose may be doubled, still administered once daily, if judged clinically necessary. For the 5 mg tablet, for dogs weighing 5 – 10 kg the standard dose is half a tablet, the double dose, one tablet. For dogs weighing 11 – 20 kg the standard dose is one tablet, the double dose is two tablets. For the 20 mg product, for dogs weighing 21 – 40 kg, the standard dose is half a tablet, the double dose one tablet. For dogs weighing 41 – 80 kg, the standard dose is 1 tablet, the double dose is two tablets.
These applications were for generic products, submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended. The reference products were Benazepril Hydrochloride Novartis 5 mg and 20 mg Tablets for Dogs, authorised in the UK since 2006. The products should not be given to dogs with evidence of cardiac output failure due to aortic stenosis, and should not be used in cases of hypersensitivity to any of the ingredients. The product should also not be used in cases of hypotension, hypovolaemia, hyponatraemia or actue renal failure, or in pregnancy or lactation. 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, the slight reactions observed are indicated in the SPC.
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 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. QUALITY ASPECTS

A. Composition

The products contain 5 mg or 20 mg benazepril hydrochloride and excipients cellulose microcrystalline, crospovidone, povidone, basic butylated methacrylate copolymer, silicon dioxide anhydrous, sodium laurilsulphate, dibutyl sebacate, silica colloidal anhydrous, stearic acid, yeast powder and artificial powdered beef flavour. The absence of preservative is justified.
The container system consists of aluminium/aluminium blister packs containing 14, 28, 56 or 140 tablets. The particulars of the containers and controls performed are provided and conform to the regulation.
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. Process validation data on the product have been presented in accordance with the relevant European guidelines. For validation studies on the finished product, two commercial batches gave satisfactory results for the 20 mg product. For the 5 mg product, three consecutive batches were analysed, all of which gave acceptable results. Until packaged, tablets are stored in metal containers lined with polyethylene bags.

C. Control of Starting Materials

The active substance is benazepril hydrochloride, an established active substance described in the European Pharmacopoeia (Ph. Eur). The active substance is manufactured in accordance with the principles of good manufacturing practice. Acceptable validation data were presented for all described methods of analysis. 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.
All excipients except the flavouring, dibutyl stearate and silicon dioxide, anhydrous are described in the Ph. Eur. Dibutyl stearate and silicon dioxide, anhydrous are monographed in the United States National Formulary. An in-house test was developed for the flavouring.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present, or used in the manufacture of this product. A Format 3 declaration states that no starting materials present a risk with regard to TSEs.

E. Control Tests on Intermediate Products

The results of tests performed for release on three batches each of the intermediate products are provided and comply with the specifications. Tests consist of analysis of appearance, colour, loss on drying, presence of impurities, particle size and dissolution. Two identity tests on benazepril hydrochloride are performed, in addition to a test on the content of benazepril hydrochloride. The specification was considered suitable for the analysis of the intermediate product.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. Control tests on the finished products include tests for appearance, identity of the active substance, water content, mean mass, content of impurities and active substance, dissolution tests, uniformity of dose and microbiological analysis. 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.

G. Stability

Stability of the Active Substance

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A five year retest period was justified.

Stability of the Finished Product

Data were supplied for two batches of the 20 mg tablets, manufactured on a commercial scale, tested under VICH conditions for thirty-six months at 5°C, 25°C/60% RH and 30°C/60%RH and for six months at 40°C/75% RH, with tablets being contained in the blister packs proposed for marketing. The products met all requirements of the proposed shelf-life, as specified in the SPC.

H. Genetically Modified Organisms

Not Applicable.

J. Other Information

The shelf-life of the veterinary medicinal product as packaged for sale is three years. The shelf-life of halved tablets is two days. The product literature recommends placing remaining halved tablets back into the opened blister pack.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, and an exemption from bioequivalence studies under 4c) of EMEA/CVMP/016/00 has been permitted, results of bioequivalence studies are not required. The SPCs of these products are identical to the reference products.
Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and the environment.

III.A Safety Testing

Pharmacological Studies

As the applicant is the Marketing Authorisation Holder for the reference products, the formulation and manufacture of the generic and reference products are identical. There is therefore no requirement for data in this section.

Toxicological Studies

As the applicant is the Marketing Authorisation Holder for the reference products, the formulation and manufacture of the generic and reference products are identical. There is therefore no requirement for data in this section.

Other Studies

As the applicant is the Marketing Authorisation Holder for the reference products, the formulation and manufacture of the generic and reference products are identical. There is therefore no requirement for data in this section.

User Safety

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. These warnings are:-

- Wash hands after use.

Pregnant women should take special care to avoid accidental exposure because ACE inhibitors have been found to affect the unborn child after oral exposure during pregnancy in humans.

- In case of accidental ingestion by children, seek medical advice immediately and show the doctor this warning.

Ecotoxicity

The applicant provided a Phase 1 environmental risk assessment in compliance with the relevant guideline, which showed that no further assessment was required. The assessment concluded that the product is intended for the treatment of dogs with congestive heart failure, that benazepril hydrochloride is converted *in vivo* to benazeprilat, a highly potent and selective inhibitor of angiotensin-converting enzyme. In addition, that the recommended dose may be doubled if clinically required, and that there is no limit on duration of treatment.
The products are not to be used in food-producing animals, and as sick animals are likely to be kept indoors, any waste material will be collected by the dog owner and disposed of with other waste. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed. There was no requirement for the evaluation of environmental risk to proceed beyond Phase 1, the use of the products will not pose a risk to the environment when used as recommended.

Withdrawal Periods

As these products are to be used in non-food producing species, there is no requirement for data in this section.

IV. CLINICAL ASSESSMENT

As this is a generic application according to Article 13, and an exemption from bioequivalence studies under 4c) of EMEA/CVMP/016/00 has been permitted, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Pharmacology

As this is a generic application according to Article 13, and an exemption from bioequivalence studies under exemption 4c) of EMEA/CVMP/016/00 has been permitted, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Tolerance in the Target Species of Animals
As this is a generic application according to Article 13, and an exemption from bioequivalence studies under 4c) of EMEA/CVMP/016/00 has been permitted, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.B Clinical Studies
Laboratory Trials
As this is a generic application according to Article 13, and an exemption from bioequivalence studies under 4c) of EMEA/CVMP/016/00 has been permitted, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Field Trials
As this is a generic application according to Article 13, and an exemption from bioequivalence studies under 4c) of EMEA/CVMP/016/00 has been permitted, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable

VI. POST-AUTHORISATION ASSESSMENTS

22 June 2017	Change in the name of a manufacturer of an intermediate used in the manufacturing process of the active substance.
07 March 2017	Introduction of a new pharmacovigilance system.
05 September 2016	Addition of a test and limits for to the active substance specification.
05 September 2016	Addition of a manufacturer of the starting material. Addition of Ph. Eur. test method and limit Addition of a Ph. Eur. test method Addition of a Ph. Eur. test method
15 August 2016	Change in the name of a manufacturer of the finished product including manufacturer responsible for batch release.
16 March 2016	Change in distributor details Change in legal entity
03 August 2015	Addition of a new manufacturer of a starting material. Re-definition of a starting material used in the manufacture of the active substance.
14 May 2015	Renewal – UK as RMS.
01 July 2014	Change of name of a manufacturer of a starting material.
30 June 2014	Change of name and address for an active substance manufacturer, deletion of active substance manufacturer and addition of two sites for quality control testing.
25 April 2014	Change in the specification parameters and/or limits of an excipient.
25 April 2014	Changes in the specification parameters and/or limits of the finished product.
27 March 2014	Changes to an existing pharmacovigilance system as described in the DDPS.

05 March 2014	Changes to the package leaflet which do not affect the SPC.
23 August 2012	To add a manufacturer with consequential changes to protocol.
12 July 2012	Update of testing monograph for active substance, several changes including changes in test procedures, tightening of specification limits, replacement of a test method, addition of new specification parameters and addition of a new specification parameter as a result of a safety or quality issue.
12 July 2012	Update of testing monograph for active substance, several changes to a preparation protocol and addition of an in-process control.
11 May 2012	Update of SPC and product literature in order to implement the outcome of an Article 34 referral.
22 February 2012	Changes in the test procedure of the finished product. (5 mg product only).
22 February 2012	Changes in the specification parameters and/or limits of the finished product. (5 mg product only).
16 September 2011	Changes to an existing pharmacovigilance system as described in the DDPS.
14 October 2010	To change the product name from **Benazepril Hydrochloride Novartis 5 mg Tablets for Dogs** to **Fortekor Flavour 5 mg Tablets for Dogs**
23 July 2010	Change in the specification parameters used in the manufacturing process of the active substance