IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

FATROBENDAN 10 mg, chewable tablets for dogs

PRODUCT SUMMARY

EU Procedure number	IE/V/0571/003/MR
Name, strength and pharmaceutical form	FATROBENDAN 10 mg, chewable tablets for dogs
Active substances(s)	Pimobendan
Applicant	FATRO S.p.A. Via Emilia 285 - 40064, Ozzano Emilia Bologna Italy
Legal basis of application	Hybrid application (Article 13(3) of Directive No 2001/82/EC)/(Article 19 of Regulation 2019/6)
Date of authorisation	19 March 2021
Target species	Dogs
Indication for use	For the treatment of canine congestive heart failure originating from dilated cardiomyopathy or valvular insufficiency (mitral and/or triscuspid valve regurgitation)
ATCvet code	QC01CE90
Concerned member states	CY, CZ, EL, ES, LT, PL, PT, SK, UK(NI)

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the Health Products Regulatory Authority (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 the relevant article of Regulation 2019/6 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

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. Qualitative and Quantitative Particulars

The product is formulated as a tablet and contains the active substance, pimobendan, and the excipients magnesium stearate, croscarmellose sodium, carmellose sodium, glycerol dibehenate, pork liver powder, and cellulose microcrystalline. The product is packaged in PVC/PE/PVdC/PE/PVC blisters sealed with thermoheated aluminium foil. The blisters are packaged in outer cardboard boxes. 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 at a licensed manufacturing site. Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is 'pimobendan for veterinary use' which is an established substance described in the European Pharmacopoeia. 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 has been provided. 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 on Intermediate Products

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 product. Satisfactory validation data for the analytical methods has been provided. Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

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

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a hybrid application and bioequivalence with a reference product has been demonstrated, the results of safety tests are not required.
The reference veterinary medicinal product cited is Vetmedin 5 mg palatable tablets for dogs (MA 102409063 - Boehringer Ingelheim Italia) which has been authorised in the EU for greater than ten years.
The safety aspects of this product are considered to be identical to the reference product.
Warnings and precautions as listed on the product literature include 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

An *in vivo* bioequivalence study was provided comparing the 5 mg strength of the produce with the reference product (Vetmedin 5 mg palatable tablets for dogs) following a single administration of each product in the test period. Blood samples to establish the plasma concentrations of pimobendan and O-desmethyl-pimobendan were taken at regular intervals until 10 hours after administration and the parameters AUC, C_{max} and T_{max} were determined. The evaluation of bioequivalence was based upon the statistical comparison of the pharmacokinetic parameters AUC and C_{max} for pimobendan and O-desmethyl-pimobendan. A 90% confidence interval was used to interpret bioequivalence data.
Results indicate that the 90% confidence interval of the ratio (Test/Reference) of least-square means from the ANOVA of the ln-transformed AUC and C_{max} for both pimobendan and O-desmethyl-pimobendan fell within the predefined acceptance limits (80 – 125%). Based on the results from this study, it was accepted that the product has been demonstrated to be bioequivalent to the reference product.

Toxicological Studies

This application was submitted as a hybrid application. Based upon bioequivalence with the reference product being accepted, the results of toxicological studies are not required. The safety aspects of this product are considered to be identical to the reference product. Warnings and precautions as listed on the product literature include those of the reference product cited and are considered adequate.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the risk to the user associated with use of this product is the same as that of the reference product. The user safety statements included in the product literature are broadly in line with those of the reference product and can be considered acceptable. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

People with known hypersensitivity to pimobendan or to any of the excipients should avoid contact with the veterinary medicinal product.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
Wash hands after use.
Advice to doctors: accidental ingestion, especially by a child, may lead to the occurrence of tachycardia, orthostatic hypotension, flushing of the face and headaches.

Environmental Risk Assessment

Phase I: The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the product is only intended for administration to a non-food producing species. It can be accepted that the environmental safety statements accepted for the reference product can be applied to this product.

Conclusion

Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

IV. CLINICAL ASSESSMENT

As this is a hybrid application and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Pharmacological Studies

An *in vivo* bioequivalence study was provided comparing the 5 mg strength of the product with the reference product (Vetmedin 5 mg palatable tablets for dogs) following a single administration of each product in the test period. Results indicate that the 90% confidence interval of the ratio (Test/Reference) of least-square means from the ANOVA of the ln-transformed AUC and C_{max} for both pimobendan and O-desmethyl-pimobendan fell within the predefined acceptance limits (80 – 125%). Based on the results from this study, it was accepted that the product has been demonstrated to be bioequivalent to the reference product.
To extrapolate the findings from the *in-vivo* bioequivalence study for the 5 mg strength product to the additional strengths of the product (1.25 mg and 10 mg tablets), a dissolution study was conducted. The dissolution profiles of the tablets were compared using three dissolution media at different pHs; 1.2, 4.5 and 7.5. The dissolution profiles were then compared for the products, with samples taken at various times. The results showed similar dissolution profiles for pimobendan in the test products.

It was accepted that the 5 mg strength product has been demonstrated to be bioequivalent to the reference product (Vetmedin 5 mg) by way of an *in vivo* bioequivalence study and that bioequivalence has been demonstrated between the 5 mg, 1.25 mg and 10 mg strength test products by way of a dissolution study.

Tolerance in the Target Species of Animals

As this is a hybrid application and bioequivalence with the reference product has been demonstrated, results of tolerance studies are not required. In addition, the applicant conducted an *in vivo* bioequivalence study in which no adverse events were observed following administration of the product to the dogs included in that study. Furthermore, the product is to be administered orally to dogs at the same posology as already approved for the reference product therefore, the tolerance profile of the candidate product is expected to be the same as that of the reference product. Consequently, the omission of target animal tolerance data was accepted. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies

As this is a hybrid application and bioequivalence with a reference product has been demonstrated, results of clinical studies were not required.

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.