ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Boehringer Pimobendan 0.75 mg/ml Solution for Injection for Dogs

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Boehringer Pimobendan 0.75 mg/ml Solution for Injection for Dogs
Applicant	Boehringer Ingelheim Ltd Ellesfield Avenue Bracknell Berkshire RG12 8YS
Active substance(s)	Pimobendan
ATC Vetcode	QC01CE90
Target species	Dogs
Indication for use	To initiate treatment of canine congestive heart failure originating from valvular insufficiency (mitral and/or tricuspid regurgitation) or dilated cardiomyopathy.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Extension application in accordance with Annex II of Directive 1084/2003/EC as amended.

I. SCIENTIFIC OVERVIEW

This was an extension application submitted in accordance with Annex II of Directive 1084/2003/EC to add a new pharmaceutical form (solution for injection), and a new route of administration (intravenous administration), to the parent product Vetmedin 2.5 mg Hard Capsules for Dogs (Vm 00015/4049), which was first authorised in the UK in 1999.

Boehringer Pimobendan 0.75 mg/ml Solution for Injection for Dogs is intended to initiate treatment of canine congestive heart failure originating from valvular insufficiency (mitral and/or tricuspid regurgitation) or dilated cardiomyopathy.

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[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 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 product contains pimobendan 0.750 mg/ml and excipients hydroxypropyl-β-cyclodextrin, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dehydrate, sodium hydroxide, hydrochloric acid and water for injections.

The container/closure system consists of a single-use 5 ml or 10 ml Type I glass vial with a rubber stopper and sealed with an aluminium cap, packed singly in a cardboard box. The particulars of the containers and controls performed are provided and conform to the regulation.

The absence of a preservative is justified.

[1] Summary of Product Characteristics

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.

The product has been manufactured according to pharmaceutical standard process. Process validation was performed on three full scale batches in accordance with the relevant European guidelines. Several in-process analyses were carried out including pH, density, filling volume and particulate contamination.

C. Control of Starting Materials

The active substance is pimodendan, an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice and in accordance with a certificate of suitability issued by the European Directorate for the Quality of Medicines & HealthCare (EDQM). The active substance is then milled at a further manufacturing site.

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 are manufactured in accordance with the specifications as described in the European Pharmacopoeia.

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 declaration in accordance with the 'Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products' is provided from the Marketing Authorisation Holder stating that the active substance and all excipients are of non-animal origin.

E. Control on intermediate products

There are no intermediate products.

F. 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 for three batches from the proposed production site have been provided demonstrating compliance with the specification. Tests include those for appearance, colour of solution, identification, extractable volume, pH, related substances and sterility.

G. Stability

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 re-test period of 60 months is justified for the milled active substance. It is noted that the certificate of suitability for the active substance manufacturer specifies a re-test period of 4 years; however, this is for the unmilled material.

Stability data on three batches of the finished product have been provided in accordance with applicable European guidelines demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. The study was conducted for 36 months at 25°C/60%RH, 36 months at 30°C/65%RH, and 6 months under accelerated conditions at 40°C/75%RH. Tests included those for appearance, colour of solution, clarity of solution, pH, assay pimobendan, degradation products and sterility for defined timepoints.

H. Genetically Modified Organisms

Not applicable

J. Other Information

The shelf life of the product as packaged for sale is 36 months. After opening the product should be used immediately and is for single-use only. Any product remaining in the bottle after withdrawal of the required dose should be discarded.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

The applicant has not presented any new data in this section of the dossier and cross refers to the data previously submitted in support of Vetmedin Capsules and Vetmedin Flavour Tablets. This is considered acceptable.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline addressing the potential exposure routes to the operator. When used as directed, the product will only be administered by veterinary professionals in a clinical environment and therefore the main route of exposure was identified as accidental self–injection. The SPC and product literature contain the following safety warning:

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline 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.

IV CLINICAL ASSESSMENT (EFFICACY)

This application is for an extension to the parent product Vetmedin 2.5 mg Hard Capsules (MA: 00015/4049). The applicant has submitted additional data to support the application for a new pharmaceutical form and administration route.

The efficacy of Vetmedin 0.75 mg Solution for Injection for Dogs can be extrapolated from that of the oral formulations Vetmedin Capsules and Vetmedin Flavour Tablets, based on the demonstration of pharmacodynamic equivalence with the originally authorised Vetmedin Capsules.

IV.A Pre-Clinical Studies

Pharmacology

The applicant conducted a single dose, two treatment, two period crossover study comparing the effect of single, therapeutic doses of Vetmedin Flavour Tablets and Vetmedin Solution for Injection on hemodynamic and electrocardiographic parameters in conscious dogs. The results are considered acceptable as a means of demonstrating pharamcodynamic equivalence. The applicant also submitted the results of two bridging data analyses based on the new pharmacodynamic equivalence study and a similar study previously submitted, which support the main pharmacodynamic study originally submitted.

The pharmacokinetics of pimobendan have previously been assessed for related products Vetmedin Capsules and Vetmedin Flavour Tablets. No new pharmacokinetic data was submitted and this was considered acceptable.

Tolerance in the Target Species of Animals

The applicant has referred to data previously submitted for Vetmedin products. Some new data was submitted including periodic safety update reports (PSURs) for Vetmedin 1.25 mg, 2.5 mg, and 5 mg Flavour Tablets for Dogs from June 2006 to January 2009. A local tolerance study looking at subcutaneous and intravenous local tolerance in dogs was also conducted. Results from the study and available data from historical toxicological studies suggest that the active substance in Vetmedin 0.75 mg Solution for Injection for Dogs, when used at the proposed dose rate and in accordance with the proposed indication, is likely to be well tolerated. The PSUR data submitted reflect the known safety profile of the active substance.

IV.B Clinical Studies

The applicant has submitted bibliographical data in support of the application that was not originally submitted in the dossier for the parent product. However, this data was previously submitted and assessed for subsequent variation applications and was therefore only summarised in the assessment. This was considered acceptable.

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.

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.

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