IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Cardisure 3.5 mg/ml Oral Solution for Dogs

PRODUCT SUMMARY

EU Procedure number	IE/V/0421/001/DC
Name, strength and pharmaceutical form	Cardisure 3.5 mg/ml Oral Solution for Dogs
Active substance(s)	Pimobendan
Applicant	Dechra Ltd Snaygill Industrial Estate Keighley Road Skipton North Yorkshire BD23 2RW United Kingdom
Legal basis of application	A hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of Authorisation/ completion of procedure	04/07/2019
Target species	Dogs
Indication for use	For the treatment of canine congestive heart failure originating from valvular insufficiency (mitral and/or tricuspid regurgitation) or dilated cardiomyopathy.
ATCvet code	QC01CE90
Concerned Member States	AT, BE, BG, CY, CZ, DK, EE, EL, FI, HR, HU, IE, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI, SK

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

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 contains pimobendan as the active substance at a concentration of 3.5 mg/ml and the excipients benzyl alcohol, glycerol, macrogol 300, povidone K90, propylene glycol, acesulfame potassium (E950) and steviol glycosides (E960).
The container/closure system consists of amber polyethylene terephthalate bottles of 42 ml and 168 ml fitted with white polypropylene child resistant caps and low-density polyethylene syringe adaptors. A 1.5 ml dosing syringe is supplied with the 42 ml bottle and a 3 ml dosing syringe is supplied with the 168 ml bottle.

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, an established active 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.
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.

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)

This application was submitted in accordance with paragraph 3 of Article 13 of Directive 2001/82/EC (a "hybrid" veterinary medicinal product). The reference veterinary medicinal product is Vetmedin 5 mg Capsules containing pimobendan as the active substance.

Pharmacological Studies
The candidate product is quantitatively and qualitatively the same as the reference product in terms of the active substance (pimobendan). However, it differs in excipients and pharmaceutical form, i.e. the candidate product is an oral solution and the reference product is a capsule.
Based upon the results from an in vivo bioequivalence study the candidate product and the reference product can be considered bioequivalent for the pharmacokinetic parameter AUC but not for the parameter Cmax. Whilst the point estimate for the ratio of test/reference product for the parameter Cmax was similar (111%), the upper limit of the 90% confidence interval for Cmax falls outside the upper bound of the pre-specified wider acceptance limit of 143% (148.9%). Based upon this result, the test and reference articles do not meet the criteria to be considered bioequivalent in terms of maximum concentration of pimobendan (Cmax).
As a result, additional information and data (including an expert report from a pharmacokinetics expert that reviewed that statistical analysis of the the pharmacokinetics data) was provided that considered the impact of this finding in terms of safety and efficacy and to justify that the candidate formulation could be considered acceptable in terms of both efficacy and safety when compared with the reference product.
Given the legal basis of this application (Art 13.3) and the findings from the in-vivo bioequivalence study and the additional information and data provided, it was accepted that in this instance, the pharmacological effects of the candidate formulation are expected to be sufficiently similar to those of the reference product to be considered the same.

Toxicological Studies

As this is a hybrid application submitted in accordance with paragraph 3 of Article 13 and based on the findings from the in vivo bioequivalence study and the addtional information and data provided, results of toxicological tests were not required. The safety aspects of this product are expected to be the same as those of the reference product. Warnings and precautions as listed on the product literature are broadly in line with those of the reference product.

User Safety
The applicant provided a user safety assessment. In view of the fact that risk for user exposure to an oral suspension (the candidate product) is likely to be greater than to a solid pharmaceutical form (the reference product), studies characterising the potential for dermal/ocular irritancy and skin sensitisation were provided. These studies indicate that the candidate product has the potential to cause skin sensitisation and as such a suitable warning and risk mitigation measures have been included in the SPC. The user safety statements are broadly in line with those of recent generics of the reference product and are generally acceptable.
Warnings and precautions as listed on the product literature are considered adequate to ensure safety to users of the product:

- Accidental ingestion, especially by a child, may lead to the occurrence of tachycardia, orthostatic hypotension, flushing of the face and headaches. To avoid accidental ingestion, do not leave the filled syringe unattended and store the bottle and used syringe in the original carton in order to prevent children from getting access to the product. Close bottle tightly with cap directly after removal of the required amount of liquid. The product must be used and kept out of sight and reach of children.
- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
- This product is a skin sensitiser. Handle this product with care to avoid exposure to the skin. Wash hands after use.
- People with known hypersensitivity to pimobendan or any of the excipients in this product should avoid exposure to the skin. In case of accidental spillage on skin, wash off immediately with soap and water.

Environmental Risk Assessment
The Applicant provided an environmental impact assessment as required. 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 application has been submitted in accordance with paragraph 3 of Article 13 of Directive 2001/82/EC (a "hybrid" veterinary medicinal product) and based on the results of the in vivo bioequivalence and the addtional information and data provided, efficacy studies were not required.
The efficacy claims for this product are expected to be equivalent to those of the reference product. In addition, it is considered that the risk to the target species will be similar for both the candidate and the reference products. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

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

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 HPRA website.
This section 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.
Changes:
None.